BASIC SCIENCES *for* ORTHOPEDICS

Prepared by Contract with Northwestern University for

THE DEPARTMENT OF MEDICINE AND SURGERY
VETERANS ADMINISTRATION

Compiled by

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Foreword

A critical survey of present-day trends in the various fields of postgraduate medical education reveals many changes, significant and far reaching in scope, which have taken place within the past 5 years. Prior to the termination of World War II, it was evident that only with the utmost economy of planning could existing medical educational facilities hope to take care of the accumulated demand for graduate training which would be made by the large group of physicians whose normal progression to the levels of residency training had been interrupted by uniformed service during the war years. In addition, the increasing emphasis which the specialty boards were coming to place upon a thorough grounding in the field of basic science as preparation for certification in the various specialties made mandatory the development of specific programs of basic science instruction in all medical schools and teaching hospitals.

Since 1946, when the Department of Medicine and Surgery of the Veterans Administration began organization of its teaching hospitals under a policy of close cooperation with top-flight medical schools throughout the country, it has been readily apparent that there was little or no coordination possible in the rapid development of the basic science training programs by individual schools and hospitals. In some schools, the material which was presented in lecture and demonstration form has aroused little more than academic interest; young physicians, asked to sit in classrooms all day with no opportunity for participation in the preparation of pathological material or the examination of patients, have become justifiably critical, weary, and discouraged. Other basic science programs have concentrated almost exclusively on the clinical approach; instruction of graduate students by means of contact with patients, with little or no formal teaching, has been the rule, and a noticeable lack of organization of the work has been the chief objection.

To fill the critical need for a carefully planned outline of all the subject material needed for basic science instruction in an orthopedic surgical training program, the Veterans Administration requested Dr. Sid John Shafer and Dr. Howard L. Compere to undertake revision, organization, and compilation of the material currently comprising the basic science course as presented by the Department of Orthopedic Surgery, Northwestern University Medical School. This publication thus represents a coordination of effort to provide a standardized foundation for orthopedic surgical basic science training, not only in Veterans Administration teaching hospitals but in any teaching hospital or medical school which may choose to utilize it.

In preparation of this material, there have been compressed within one volume the more important and essential facts with which the well-trained

orthopedic surgeon must be thoroughly familiar. The material is not, however, presented as a finished course of lectures; rather is it offered as a skeletal framework around and upon which the young surgeon may mold the sum total of his knowledge of orthopedic surgery. Instruction in the basic sciences, as applied to any medical or surgical specialty, must be compounded as a blend of the didactic and the clinical; it is our hope and belief that, by judicious study of the literature and alert attendance in the clinic and at the bedside, each student may erect, upon the foundation of these pages, the fully rounded structure of knowledge characteristic not only of the well-trained, but of the well-educated, orthopedic surgeon.

PAUL B. MAGNUSON, M. D.,
Chief Medical Director, Veterans Administration.

DECEMBER, 1948.

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General

I. MUSCLE METABOLISM

A. CHEMICAL PHYSIOLOGY OF MUSCULAR CONTRACTION

There are two phases in the contraction cycle, an *anaerobic* (*anoxidative*) *phase* and an *aerobic* (*oxidative*) or *recovery* phase, during which the muscle is restored to its previous state. The lactic acid concentration at which complete fatigue of skeletal muscle ensues (lactic acid maximum) is from 0.3 to 0.6 percent. The lactic acid is derived from the break-down of glycogen. As the lactic acid concentration rises, the carbohydrate stores diminish. Yet, the onset of fatigue is not due to the exhaustion of the glycogen stores, for the muscle fails to contract before the latter have disappeared. It is more likely that the high acidity inhibits the enzymes through whose action glycogen break-down is brought about. Phosphoric acid also accumulates in a muscle contracting in the absence of oxygen. The phosphoric acid production rises rapidly during the earlier contractions, soon reaches a maximum, and then ceases.

B. CHEMICAL CHANGES ASSOCIATED WITH MUSCULAR CONTRACTION

The first reactions are the break-down of *adenosine triphosphate* to *adenylic acid* and *phosphoric acid* which becomes engaged simultaneously in the phosphorylation of glycogen; fructose *diposphate* is formed. *Phosphorocreatine* next breaks down, yielding *creatine* and *phosphoric acid* which immediately joins with the adenylic acid formed in the previous reaction, adenosine triphosphate being resynthesized. The fructose diphosphate gives rise to *dihydroxyacetone phosphoric acid* and phosphoglyceraldehyde. The total energy derived from the conversion of glycogen to lactic acid is utilized for *phosphocreatine resynthesis* which takes place partly (about ⅓) in the anaerobic phase and partly (about ⅔) in the aerobic phase. The phosphoric acid for the resynthesized phosphocreatine is obtained from the break-down of phosphopyruvic acid by way of adenosine triphosphate. Thus phosphate borrowed from adenosine triphosphate for the phosphorylation of glycogen is given up for the resynthesis of phosphocreatine. Of the lactic acid formed, a part is resynthesized to glycogen, the energy for the resynthesis being derived from the oxidation of the remainder of the lactic acid. In *fatigue*, the accumulation of lactic acid slows and then arrests the glycogen→lactic acid break-down and, as a consequence, phosphocreatine resynthesis is prevented. *Lactic acid production, therefore, though not directly furnishing the energy for contraction, serves to "wind up" the contractile mechanism* or, if one may compare it to a storage battery, to

recharge it. *Adenosine triphosphate is the immediate source of the energy for the contraction.* The reversible reactions are dependent upon an enzyme system in the muscle; adenosine triphosphate, in the presence of the magnesium ions, acts as a coenzyme serving as an intermediary in the transference of phosphate.

(*a*) Adenosine triphosphate	Phosphoric acid plus Adenylic acid	Energy for contraction
(*b*) Phosphocreatine	Creatine plus Phosphoric acid	Energy for resynthesis of adenosine triphosphate
(*c*) Glycogen to lactic acid		Energy for resynthesis of phosphocreatine
(*d*) Oxidation of part of lactic acid (about 1/5)		Energy for resynthesis of the remainder of the lactic acid to glycogen

C. LACTIC ACID PRODUCTION DURING EXERCISE

The lactic acid produced in a short bout of strenuous exercise may amount to as much as 3 gm. per second, and its concentration in the blood rise as high as 0.2 percent. The lactic acid, though buffered by the muscle protein thus



$H^+ + L^- +$	$Na^+ + P^- \rightarrow$	$Na^+ + L^- +$	HP
lactic acid	sodium proteinate	sodium lactate	acid proteinate undissociated

and to a less extent by phosphates and bicarbonates, causes a sufficient change in blood reaction to stimulate powerfully the respiratory center. Large amounts of carbon dioxide are "blown off" from the lungs.

II. AUTOMATIC NERVOUS SYSTEM

The autonomic nervous system consists of all the neurons whose cell bodies are situated outside the central nervous system (excepting those of the posterior root ganglia and special senses) and the efferent neurons functionally connecting these outlying neurons with the spinal cord and brain.

A. REFLEX ARC ARRANGEMENT

The function of the autonomic nervous system is to control the activity of unstriated muscle and gland tissue throughout the body.—These structures are innervated according to the plan of the reflex arc, in that a set of afferent fibers enter the central nervous system and there transmit impulses to a set of efferent fibers.

The arrangement of the *autonomic reflex arc* differs from that of the somatic reflex arc in that the efferent limb nerve passes directly as a single fiber from the central nervous system to the effector organ (smooth muscle or gland); it always is interrupted at some point in its course toward the periphery, so that it consists in every instance of two fibers, one extending from the center to some point where it ends by synapse and a second fiber which proceeds from that point to the structure to be innervated. Hence it is that the *two fibers* of the *efferent limb* have been termed *pre- and postganglionic* respectively.

All the *connector fibers* (*preganglionic fibers*) are called *"white,"* since they have a *myelin sheath.* All the *excitor fibers,* otherwise known as *postganglionic,* are "gray," that is, they have *no myelin sheath.*

B. SUBDIVISIONS

The autonomic system is subdivided according to the anatomical grouping of the connector fibers. The latter emerge from the central nervous system in *three regions:* (1) Directly from the brain, (2) from the thoracolumbar region of the spinal cord, and (3) from the sacral region of the cord.

1. Sacral Outflow (Parasympathetic). The *sacral outflow* arises from the second and third (and often also the fourth) sacral segments of the spinal cord. The fibers from these segments unite to form the *pelvic nerve,* which is often a plexiform structure rather than a unified nerve trunk. These sacral connector fibers pass uninterruptedly to the vicinity of the various pelvic organs which they supply.

a. Functions. The sacral autonomic supply is *motor to* (stimulates) the large bowel below the level of the hepatic flexure, to the urinary bladder, and to the muscle fibers about the prostate gland. It is *inhibitory* to the sphincters of the bowel and bladder, and to the blood vessels of the external genitals. The genetic function of the sacral outflow is to promote nutritive

and reproductive processes. The sacral autonomic fibers have no synaptic relation with the sympathetic trunks or with any somatic nerve trunks.

2. Thoracolumbar Outflow (Sympathetic). The sympathetic (thoracolumbar) nerve fibers all arise from the spinal cord between the first thoracic and the second lumbar segments inclusive. In the "gap" (L_3 to S_1) between this thoracolumbar outflow and the sacral outflow, the spinal nerves *as they emerge* from the spinal cord contain no autonomic fibers whatever. A short distance *outside* the spinal canal, however, these spinal nerves (L_3 to S_1) are joined by sympathetic fibers, but the latter are all derived from the restricted thoracolumbar region mentioned (T_1 to L_2); they reach the neglected "gap" segments (L_3 to S_1) by passing downward in the sympathetic trunk.

In general, the sympathetic fibers follow the cerebrospinal nerve trunks to reach the somatic regions; to reach visceral regions they either form independent pathways or follow the blood vessels.

C. SYMPATHETIC TRUNK

All the sympathetic connector fibers pass from the spinal cord to the sympathetic trunk. The latter extends all the way from the base of the skull to the coccyx. The sympathetic trunk carries the thoraco-lumbar fibers upward to the craniocervical region and downward to the lumbosacral region, thus ensuring innervation of these parts by the sympathetic division of the autonomic system.

1. Sympathetic Innervation of Upper Limb. The sympathetic connector fibers for the *upper limb* arise in several of the midthoracic spinal cord segments (*about T_4 to T_9*), extend up the sympathetic trunk and terminate in the *inferior cervical ganglion* by synapse with the cell bodies of the excitor fibers. The latter join the roots of the brachial plexus and are distributed with the branches of the plexus throughout the upper limb.

2. Sympathetic Innervation of Lower Limb. The lumbar and sacral sometic nerves which supply the lower limb (*L_4 to S_3*) are all below the lower limit of sympathetic outflow and therefore do not obtain any sympathetic elements directly from the spinal cord. There is, however, a chain ganglion corresponding to each of these nerves, and the sympathetic component of the nerve is derived from this ganglion; *all preganglionic fibers originate in and above the second lumbar segment (T_{10} or T_{12} to L_2) and descend in the sympathetic trunk to terminate in the chain ganglia (L_2 to S_3) below that level.* The excitor fibers, after passing these ganglia to the lumbar and sacral nerves, are distributed by way of the lumbosacral plexus throughout the lower limb.

D. CONTRAST BETWEEN SYMPATHETIC AND PARASYMPATHETIC DIVISIONS

The parasympathetic subdivisions of the autonomic system supply in general *only splanchnic* regions, for anatomically they are not distributed to any portion of the purely somatic regions, such as the thoracic and abdominal parietes and the extremities. *The sympathetic division, on the contrary, is distributed to all regions of the body, both splanchnic and somatic. The chief purpose of the sympathetic innervation in somatic regions*

is to control blood vessels, sweat glands, and erector pili muscles; both motor and inhibitory control of each of these functions resides in the sympathetic system. There are no pathways by which fibers belonging to either the cranial or the sacral outflow may reach the blood vessels of the extremities or the somatic portion of the trunk.

E. CHEMICAL MEDIATORS OF AUTONOMIC ACTIVITIES

1. Sympathin. Sympathin is a substance which is formed at the junction of sympathetic nerve fibers and smooth muscle cells. It has been shown that sympathin and adrenalin are one and the same substance.

2. Acetylcholine. Parasympathetic nerve impulses appear to liberate a chemical substance in an analogous manner at the nerve endings. The substance is apparently acetylcholine, which is formed constantly in small amounts in parasympathetic nerves under normal conditions in the body—the amount being considerably increased by parasympathetic nerve stimulation.

3. Adrenalin. The sympathetic substance (*adrenalin*) secreted at one point in the body may be carried by the blood stream to distant parts, thus producing a *widespread effect.* The *parasympathetic substance* (acetylcholine) spreads to neighboring cells, but it produces a more *localized response* than the sympathetic substance because it is very unstable and is *rapidly destroyed* in the body by a *specific enzyme, cholinesterase. Eserine,* which is said to "stimulate" parasympathetic nerves, in reality augments their action by interfering with cholinesterase and thus preserving the aceylcholine formed. *Atropine,* which is said to "paralyze" parasympathetic nerve endings, acts by preventing access of acetylcholine to the effector cells.

4. Sensitivity to Adrenalin Following Sympathectomy. When sympathectic denervation is accomplished by dividing only the preganglionic nerve fibers, the post[illegible]
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tiveness is much *more marked.*

F. VASOMOTOR SYSTEM

The vasomotor system is the system of nerves which regulates the caliber of the blood vessels throughout the body. In addition to its constant tonic activity, the *vasomotor system of nerves serves to adjust the blood vessels of the body as a whole in accordance with varying conditions and to adapt the vascular beds in the various regions to the local needs.*

The nervous control of the blood vessels is based upon the reflex arc. The vessels over which the vasomotor system has the greatest influence are the *arterioles.*

The capillaries are subject to nervous influence to some extent, but certainly in a much lesser degree than the arterioles and venules. *The capillary response is largely induced by local chemical factors and by the marked hydrostatic effect on the capillaries* of any changes in the caliber of the arterioles, rather than by nerve influences acting directly on the capillaries themselves.

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4. Sensitivity to Adrenalin Following Sympathectomy. When sympathectic denervation is accomplished by dividing only the preganglionic nerve fibers, the postganglionic neurons do not degenerate and the sensitiveness of the effector organs to adrenalin and sympathin which results is only *moderate* in degree. When the *postganglionic fibers* are divided, the resultant sensitiveness is much *more marked.*

F. VASOMOTOR SYSTEM

The vasomotor system is the system of nerves which regulates the caliber of the blood vessels throughout the body. In addition to its constant tonic activity, the *vasomotor system of nerves serves to adjust the blood vessels of the body as a whole in accordance with varying conditions and to adapt the vascular beds in the various regions to the local needs.*

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1. Vasoconstrictor Fibers. The efferent pathways of this reflex system are the nerve fibers of the autonomic system, both sympathetic and parasympathetic division. Certain of the efferent vasomotor nerves, in fact the majority, induce constriction of the vessels they supply. *The vasoconstrictor fibers belong exclusively to the sympathetic portion of the autonomic system and are distributed to all parts of the body.*

The sympahetic trunks carry vasomotor fibers from the restricted thoracolumbar source upward and downward to supply the neglected regions.

a. Distribution of Vasoconstrictor Fibers. The sympathetic vasoconstrictor fibers, after emerging from the thoracolumbar spinal cord, may follow *any convenient route* to reach the various parts of the body which they supply. The vasoconstrictor fibers for the various regions of the body are distributed in the manner described for the sympathetic nerve fibers. In general, the vasomotor fibers supplying somatic regions follow the corresponding cerebrospinal nerve pathways, whereas those supplying visceral structures accompany the blood vessels.

b. Upper Limb Sympathectomy. The *inferior cervical ganglion* contains all the cell bodies of the postganglionic vasoconstrictor fibers for the upper extremity, and removal of the ganglion for relief of circulatory deficiency in the limb leads to degeneration of these fibers. As a result of this denervation, sensitiveness of the blood vessels of the part to the physiological amounts of adrenalin normally in the blood stream develops after a period of about 7 or 8 days.

Division of the preganglionic fibers has been widely employed in place of ganglionectomy. The clinical results have been reported to be better following the preganglionic operation.

c. Lower Limb Sympathectomy. The synapses of the vasoconstrictor fibers for the lower extremity are scattered over a number of chain ganglia (from about L_4 to S_4 or S_5) instead of concentrated in one ganglion, as in the case of the upper limb. In lumbar ganglionectomy for the relief of circulatory deficiency in the lower extremity, only the second to fourth lumbar ganglia are removed as a rule, the fifth lumbar and all the sacral ganglia with their postganglionic neurons remaining intact. Therefore, the greater number of the postganglionic vasomotor fibers escape degeneration, and among those which escape are the fibers which supply the more peripheral parts of the limb via the sciatic nerve. Marked sensitivity to adrenalin does not develop in this region.

2. Vasodilator Fibers. The dilators arise not only from the sympathetic but also from the parasympathetic portions of the autonomic system, for there are vasodilator fibers in some of the cranial, the thoracolumbar and the sacral efferent nerves. Though the thoracolumbar portion of the cord supplies both constrictor and dilator fibers, the former are far more numerous and more active; the sympathetic dilators seem to perform very little function under normal conditions, vasodilatation being brought about in most cases by diminished activity of the vasoconstrictor fibers.

3. Chemical Control of the Vasomotor System. The vasomotor center is subject to chemical influences. *Oxygen lack, carbon dioxide excess, or increased acidity of the blood* from whatever cause affects the center,

stimulating it, and *induces thereby general vasoconstriction.* Changes contrary to these cause general vasodilatation.

Certain *hormones,* such as *adrenalin* and *pituitrin,* affect the tone of the blood vessels, but they *have their action peripherally* and not upon the vasomotor nerve center or nerve pathways.

G. OPERATIVE TREATMENT OF PERIPHERAL ISCHEMIA

After the sympathetic nerve supply of an extremity has been permanently interrupted, the temperature of the part is found to vary more with the external temperature than normally, and even to vary more with the external temperature than with the body temperature.

After the sympathetic supply has been cut off, sudden alterations in the caliber of the peripheral arteries cannot occur. All the circulatory changes are more gradual and are influenced by external stimuli rather than by controlling mechanisms within the body.

1. Skin Temperatures. Normally there is a slight diurnal rise and fall of the surface temperature as a result of alterations in the peripheral circulation.

2. Vasoconstrictor Tone. In the extremities there is a vasoconstrictor gradient below the elbows and knees, vasomotor tone being increasingly stronger toward the periphery with the result that the fingers and toes are the coolest points on the body surface.

The four principal methods available for inducing vasodilation (sympathetic paralysis) *in order to distinguish vascular spasm from organic blockage are:* (1) *novocaine nerve block,* (2) *general anesthesia,* (3) *hot baths and* (4) *injection of foreign protein intravenously.*

3. Tests for Sympathetic Denervation. The following tests may be used postoperatively to determine the completeness of sympathectomy:

a. Absence of reflex sweating on exposure to heat.

b. Absence of gooseflesh (pilomotor muscle response) on application of ice to the skin.

c. Absence of temperature change or visible cutaneous change on the injection of foreign protein.

d. Marked vasoconstriction (visible color change) following intravenous injection of 40 to 60 drops per minute of 1:250,000 adrenalin solution.

e. Injection of peripheral nerves with novocaine.

4. Periarterial Neurectomy. After periarterial neurectomy the part feels *warmer than normally,* the arteries being evidently more dilated than before. The degree and duration of this effect varies. In man it is observable for about 14 days, though some less conspicuous circulatory changes in the part are detectable for some weeks longer. Very likely the longer the segment of artery denervated, the longer will the hyperemia persist.

Thrombophlebitis can cause harmful reflex vascular disturbances which have proved amenable to treatment by interruption of sympathetic pathways.

Reflex Segmentary Arterial Spasm. Physical trauma to a large artery without thrombosis, embolism, laceration, or other resultant organic lesion of the vessel can cause marked segmentary arterial spasm.

The arterial spasm has been generally attributed to overaction of the sympathetic vasomotor nerves. Some type of sympathectomy would probably prove effective, but equal benefit should be obtainable by the use of regional blocking of the nerve trunks or roots with procaine hydrochloride.

Causalgia occurs most frequently in association with partial lesions of large nerves, particularly the median and sciatic. It would seem more likely that the median and sciatic nerves are involved so often because they contain such a large number of sensory and vasomotor fibers and because in the regions which they supply vasomotor control is exceptionally active.

The vasodilator function of the sensory neurons of the *cerebrospinal* system appears to be closely related to causalgia. In causalgia the stimulus of the sensory branch of the neuron in this axon reflex is probably intraneural fibrosis resulting from injury.

The fibrosis which initiates the axon reflex vasodilatation probably does not directly produce pain. The pain felt at the periphery is perhaps excited by the engorged state of the small blood vessels, the distended conditions of the latter stimulating sensory nerve endings in or near the blood vessel walls. It is probable that in addition to this inherent vascular sensibility there is abnormal stimulation of the ordinary pain and temperature endings of the skin by the local congestion.

In causalgia the dilatation of the arteries and larger arterioles produced by sympathectomy leads to constriction of the smaller vessels; the affected part becomes less red or even paler in appearance, though its temperature becomes even higher because of the increased caliber of the afferent blood channels.

No overactivity of the sympathetic system itself is postulated as a part of the mechanism producing causalgia. It seems likely, however, that the distressing local sensory disturbances would tend to increase the sympathetic tone in the region reflexly to some extent. Evidence in support of this idea is the fact that profuse sweating of the affected part is a characteristic feature of causalgia, and sweating usually occurs only as a result of sympathetic stimulation. However, any sympathetic overactivity in causalgia cannot be very extreme.

H. THEORIES OF REFERRED PAIN

It has been shown, that stimulation of visceral sensory nerves may reflexly produce changes in somatic parts which give rise to pain. This observation does not pertain to the subject of referred pain or visceral pain because these types of pain occur in viscera after section of the anterior roots and these pains are ameliorated only when the sensory nerves to the somatic parts are blocked and the pain stimulus is severe. This leaves three hypotheses for visceral referred pain.

1. Lange-Ross Hypothesis. Lange-Ross hypothesis maintains that referred visceral pain is due to the diffusion of visceral impulses in the cord in such a manner that they excite the secondary somatic pain neurons.

2. Mackenzie Hypothesis. Mackenzie hypothesis maintains a similar diffusion except that the visceral impulses do not give rise to pain directly but irritate the secondary somatic pain neurons so that impulses coming in over the primary sensory neurons cause pain. This may cause an

"irritable focus" in the cord, so that every functional activity of the cord is hyperexcitable. The "irritable focus" may persist after the disease has subsided. This idea of an "irritable focus" is analogous to Livingston's concept of a "vicious circle" which arises in causalgia (peripheral nerve injuries) in an "internuncial neuronal pool" due to chronic irritation of sensory nerves and causes disturbances of function and peripheral changes and even in the brain (fixation on a phantom limb) or a site far removed from the original focus of irritation.

3. Head's Law. Visceral pain impulses pass to the cord over primary pain fibers and make connections with their respective secondary pain neurons which, in turn, make connections with tertiary neurons in the thalamus for reaching the sensorium in the cerebral cortex. The cerebral cortex refers the pain to or interprets the pain as coming from the spinal segment which the pain impulses from the viscus originally enter. The cerebral interpretation is made in default of sharper localization, or on the basis of "Head's Law." This law states that the brain refers a sensory impulse coming in from an area of low sensibility to an area of higher sensibility. With a process of training or conditioning, a subject in time may learn to refer visceral pain to the appropriate site in the viscus. The localization can never be as discriminative in the alimentary tract as in the skin and soma because of the relative poverty of nerve endings, because the gut was originally a midline organ and hence there may be some bilateral overlap, and because several viscera may be innervated from the same spinal segments. This latter theory simplifies and rationalizes referred pain in visceral disease. There is only one system of pain nerves; the only difference is that some innervate the skin, some the deeper somatic tissues, and some the visceral. Referred pain represents cerebral misinterpretation or a substituted interpretation. In view of its lack of training, the cerebrum does the best it can to provide a source of origin. This phenomenon is exemplified by *allocheria* (other handedness).

III. RESPIRATION

A. RESPIRATORY EXCHANGE

The processes which constitute the phenomenon of respiration are commonly divided into two groups. *External respiration is the term applied to the interchange of oxygen and carbon dioxide between the blood and the pulmonary alveoli, internal respiration representing the transportation of these gases in the blood stream and their interchange between the blood and tissues.*

OXYGEN TRANSPORT

Only a small amount of oxygen is carried by the blood in simple physical solution (0.25 to 0.3 volume percent in arterial blood and 0.1 volume percent in venous blood). By far the greater part exists in loose combination with hemoglobin, a combination which is remarkable in that it enables the blood not only to abstract from the alveolar air an adequate supply of oxygen but also permits the diffusion, through the capillaries, of as much as is necessary for tissue oxidation processes.

The volume of oxygen taken up by the blood when it is exposed to atmospheric air, that is, *the oxygen capacity,* is *dependent upon the hemoglobin content of the blood.* The maximum amount of oxygen which can combine with 1 gm. of hemoglobin has not been determined, the commonly quoted value of 1.34 cc. as estimated by Huffner being probably inaccurate. The matter is one of considerable import, since, the oxygen capacity being dependent upon the hemoglobin content, exact knowledge regarding the oxygen capacity of 1 gm of hemoglobin would allow the exact determination of the hemoglobin concentration from the oxygen capacity of the blood. It is now recognized that the hemoglobin content of the blood of normal adults may exhibit a diurnal variation amounting to as much as 20 to 30 percent of the average concentration, resulting in similar variations in the oxygen capacity of the blood. The normal range of the latter factor has been estimated to be from 16 to 24 volumes percent.

The actual oxygen content of the blood, or the amount of oxygen which combines with hemoglobin, varies with the oxygen tension, the carbon dioxide tension, and the temperature. The carbon dioxide tension and the temperature remaining constant, an increase or decrease in oxygen tension is associated with a corresponding alteration in hemoglobin saturation with oxygen and hence in the oxygen content of the blood; the oxygen tension and temperature remaining constant, an increase in the carbon dioxide tension is associated with a decrease in the saturation of hemoglobin; the oxygen tension and carbon dioxide tension remaining constant, an increase in temperature is associated with a decrease in hemoglobin saturation.

These properties are peculiarly favorable in the physiological activity of hemoglobin in the body. *In contact with alveolar air, where the oxygen tension is relatively high and the carbon dioxide tension relatively low, oxygen is readily taken up by the venous blood, whereas it is equally readily given up by the arterial blood in the tissues where the oxygen tension is low and the carbon dioxide tension and temperature relatively high.*

The degree of oxygen saturation of the blood may be expressed as follows:

$$\frac{\text{Oxygen content}}{\text{Oxygen capacity}} = \frac{18.6}{20.0} = 93 \text{ percent.}$$

The oxygen content of normal arterial blood has been variously estimated at from 15 to 23 volumes percent, that of venous blood being from 10 to 18 volumes percent and the *average value for arterial blood being 18.5 and that for venous blood 15 volumes percent.* The oxygen exchange in the tissues is dependent upon the oxygen content of the blood (oxygen capacity and hemoglobin saturation), the rate and volume of blood flow, and the efficiency of the peripheral (capillary) circulation. The coefficient of oxygen utilization by the tissues is an expression of the resultant of these various factors and is determined as follows:

$$\frac{\text{Arterial oxygen-venous oxygen}}{\text{Arterial oxygen}} = \frac{18.5}{18.5-15.0} = \frac{3.5}{18.5} = 18.9 \text{ percent.}$$

This figure varies with alterations in the metabolic activity of the tissues as well as with variations in the factors enumerated above.

B. ANOXIA

Anoxemia, meaning oxygen deficiency in the blood, and the more general term anoxia, meaning oxygen deficiency, should properly be applied to any condition or insufficiency of tissue oxidation processes.

1. Types. According to the factors involved, Barcroft has differentiated three types of anoxemia or anoxia and Peters and Van Slyke have added a fourth. These have been termed (a) anoxic anoxia, (b) anemic anoxia, (c) stagnant anoxia, and (d) histoxic anoxia.

a. Anoxic Anoxia. This group includes conditions characterized by normal oxygen capacity but diminished oxygen tension in the arterial blood, with a consequent varying degree of hemoglobin unsaturation.

(1) High altitudes.
(2) Rapid, shallow respiration.
(3) Mechanical interference with oxygen absorption.
(4) Congenital heart disease.

b. Anemic Anoxia. This type of anoxemia is characterized by a diminution in the oxygen capacity of arterial blood due to a decrease in the amount of functioning hemoglobin.

(1) Anemia.
(2) Carbon monoxide poisoning.
(3) Methemoglobinemia.
(4) Sulfhemoglobinemia.

c. Stagnant Anoxia. Stagnant anoxia is due to circulatory inefficiency, the rate of blood flow through the tissues being retarded with resulting in-

crease in the percentage volume of oxygen removed from the blood in its passage through the capillaries. It is observed most commonly in circulatory failure associated with decompensated heart disease, in shock, and in conditions associated with vasospastic phenomena, such as Raynaud's disease.

d. Histotoxic Anoxia. Histotoxic anoxia is a term suggested by Peters and Van Slyke to indicate a condition in which the oxygen supply is normal in every respect but the degree of oxygen utilization by the tissues is diminished because the tissue cells are poisoned in such a manner that they cannot use oxygen properly.

IV. COAGULATION OF BLOOD

A. CLOTTING MECHANISM

In the intricate mechanism underlying the coagulation of blood the following substances take part: (1) *Prothrombin,* (2) *thrombin,* (3) *thromboplastin* (or *thrombokinase*), (4) *ionized calcium,* and (5) *fibrinogen.* By the action of thromboplastin, prothrombin, which is inactive, is converted in the present of calcium ions into the active thrombin. Thrombin, an enzyme, then acts upon the soluble fibrinogen of the plasma to convert it into insoluble fibrin, forming threads in which the solid elements of the blood are enmeshed. Thus the clot is formed.

In normal circumstances the blood remains fluid in the vessels, most probably because thromboplastin is present in circulating blood in only very small amounts and, as a consequence, the active enzyme thrombin is not produced and fibrin is not formed. Any small amount of thrombin which might arise in the blood is neutralized by an antithrombin. This latter material, the so-called *normal antithrombin* of the plasma, is present in low concentration in blood.

When the blood is shed, thromboplastin is liberated from the injured tissues or from the fragmentation of platelets; thus the clotting mechanism is initiated.

The clotting process is outlined in its simplest possible terms in the following scheme.

Prothrombin plus thromboplastin plus calcium equals thrombin
Thrombin plus fibrinogen equals fibrin

Thus, only four *primary factors,* prothrombin, thromboplastin, ionized calcium, and fibrinogen, are required for the coagulation of blood.

B. PROPERTIES OF PROTHROMBIN, THROMBIN, AND OF THROMBOPLASTIN

Prothrombin and thrombin are carbohydrate-containing proteins. At a pH of 7.0 prothrombin and thrombin are highly soluble in water or physiological saline, it being possible to prepare a 60 percent solution of either material.

Quick has secured evidence that prothrombin is a complex, consisting of two components (A and B) combined through calcium. Component A is reduced, presumably through oxidation, by ovalate. Component B is destroyed by dicumarol and possibly also as a result of a deficiency of vitamin K. Component A disappears from stored plasma. In hypoprothrombinemia it is usually only component B which is reduced.

The origin of prothrombin. The *liver* is probably the chief source of prothrombin, although experiments also point to its being produced to some extent as well by the bone marrow. The production of prothrombin is governed by vitamin K.

Thromboplastin is present in all tissues, *lung* and *brain* being especially rich sources. It is soluble in fat solvents and is identical with or closely allied to the phospholipid *cephalin.*

C. HEMOSTATIC AGENTS

Fibrin foam with *thrombin* is an effective hemostatic agent in the liver, peritoneal cavity, abdominal wall, kidney, and lung. Only a *slight tissue reaction* is *elicited,* and the amount of fibrous tissue due to the presence of the fibrin foam with thrombin is very small. The fibrin foam with thrombin is *absorbed* in about *5 weeks* and sometimes in a shorter interval.

The tissue reaction to soluble cellulose with thrombin and fibrin foam with thrombin are about the same.

V. KIDNEY FUNCTION

The chief function of the kidneys is to remove from the body waste and other undesirable substances and whatever water and solid material may have been formed in or introduced into the body in excess of the quantity required. They constitute an important route of elimination of certain drugs, poisons, and other toxic agents. Formation of ammonia by the rental tubular epithelium and regulation of the excretions of anions and cations play an important part in the regulation of the acid-base equilibrium. By virtue of these functions, the kidneys also play an essential role in the regulation of water balance and the osmotic equilibrium between the blood plasma and the tissue fluids and cells. The uriniferous tubule is the functional unit—there being about 1,200,000 in each kidney. From a physiological standpoint, the activity of the glomerulus must be considered apart from that of the tubule.

A. GLOMERULAR FILTRATION

The work of Richards and his associates substantiated the hypothesis of glomerular filtration proposed by Ludwig and demonstrated conclusively that glomerular urine formation is dependent upon circulatory conditions in the glomerular capillaries (pressure and rate and volume of blood flow). These investigators have demonstrated another fact of great significance: namely, that "the number of glomeruli through which the blood flows and hence which function at any one time may be a fraction only of the total number of glomeruli in the kidney" and that, therefore, "the extent of filtration surface in the kidney is variable and a factor which must be of major importance in the adjustment of renal function to excretory requirement."

Glomerular urine is formed by a process of filtration alone. The *effective filtration pressure* is the resultant of the blood pressure in the glomerular capillaries and the opposing forces of the colloid osmotic pressure of the blood plasma and the tension within Bowman's capsule (capsular pressure). The mean glomerular pressure may be regarded as about 50 percent of the mean systemic arterial pressure (90 mm. Hg), thus averaging about 45 mm. Hg. This is subject to regulation by variation in the relative degree of constriction of the afferent and efferent arterioles of the glomerulus. In addition to the influence of these pressure factors, the volume of glomerular filtrate is influenced significantly by (1) *the surface area of the filter* (glomerular capillary surface, normally 1.56 sq. m.) and (2) *the minute volume flow of blood plasma over this surface* (normally about 700 cc. of plasma or 1,200 cc. of blood per 1.73 sq. m. of body surface). These factors are affected by such conditions as glomerulonephritis, extensive destructive lesions of the kidneys, advanced nephrosclerosis, and, at times, congestive

All these extrarenal factors must be taken into consideration when studying renal function on the basis of the quantitative relationship between water supply and the urine volume. Ordinarily, the latter is simply compared with the fluid intake. The total water supply, in persons on an average diet, exceeds the fluid intake by about 700 gm.; in the absence of the pathological factors mentioned, the water loss exceeds the urine volume by approximately the same amount. Therefore, under such circumstances, *the consideration of fluid intake as total water supply and urine volume as* total water elimination involves an error of approximately only 5 percent.

2. Chloride. The kidneys play an important part in the maintenance of the chloride balance of the body. *Normally the organism is in chloride equilibrium, the quantity ingested being practically balanced by that excreted in the urine (average, 10 to 16 gm. in 24 hours), as sodium chloride.* This salt, existing in high concentration in all body fluids, exerts an important influence upon osmotic processes. It consequently constitutes one of the "threshold" substances of the urine, being eliminated normally only if its concentration in the blood exceeds the threshold value.

The study of the ability of the kidneys to excrete chloride may be approached from two angles: (1) The determination of the chloride content of blood plasma and (2) the determination of the chloride content of the urine following the ingestion of a known quantity of sodium chloride.

3. Nonprotein Nitrogen. Reference should be made to Todd and Sandford or Levenson and McFate for study of the various laboratory tests used in renal function determination.

4. 17-Ketosteroids. Some of the *adrenal cortex hormones* are excreted in the urine as 17-ketosteroids, particularly as beta-17-ketosteroids. It is believed that in the female practically all and in the male about two-thirds of the urinary 17-ketosteroids originate in the adrenal cortex. The determination of urinary 17-ketosteroids, including separation of the alpha and beta fractions, has therefore been widely employed in the clinical study of adrenal cortex function and often yields information of considerable diagnostic value.

E. CHEMICAL FINDINGS IN UREMIA

The term "uremia," as employed here, refers to that symptom complex which is associated with retention in the blood of urinary waste products and which is dependent fundamentally upon marked interference with the functional activity of the kidneys and with the consequences of such interference. It does not include so-called prerenal azotemia (nitrogen retention), which may resemble true uremia in several respects but which depends upon factors which may operate in the absence of renal disease or serious renal functional impairment.

1. Renal Function. Uremia is accompanied by evidences of advanced renal functional impairment. Clearance values are extremely low, the urea clearance being usually less than 5 percent of the average normal. Phenosulfonephthalein elimination may range from 0 to 10 percent in two hours and is usually 0 in the 15-minute specimen in the fractional method. There is marked elevation of the nonprotein nitrogenous constituents of the blood, the total nonprotein nitrogen concentration being usually well over 100 mg.

per 100 cc., the urea nitrogen over 70 mg., and the creatinine above 5 mg. The urine volume may be normal or even increased but is usually lower than it was during the period of compensation. Regardless of the urine volume, the urinary specific gravity tends to be fixed at a relatively low level, between 1.007 and 1.012 at maximum concentration (nonprotein urinary specific gravity).

2. Plasma Protein and Albuminuria. If the plasma protein concentration has been previously low it tends to increase, particularly in chronic glomerulonephritis, in which condition the plasma protein concentration may return to normal during this stage. This is due largely perhaps to the associated dehydration and hemoconcentration. It may be dependent in part upon the diminished elimination of albumin in the urine which not infrequently occurs as the chronic active stage of glomerulonephritis progresses into the terminal stage of uremia. This is due presumably to the complete occlusion of increasingly large numbers of glomeruli with consequent diminution in the large numbers of glomeruli with consequent diminution in the abnormal filtration surface area.

3. Acid-Base Balance. Advanced renal failure results almost invariably in a state of acidosis, which is therefore an almost invariable manifestation of the uremic syndrome.

4. Dehydration. Because of the impaired concentrating ability of the kidney, the excretion of salts in the urine necessitates the elimination of increased quantities of water. This relative polyuria is an important cause of dehydration in chronic nephritis.

5. Plasma Chloride. In the majority of cases, the plasma chloride concentration is somewhat diminished. This is perhaps due largely to vomiting but is also contributed to by deficient intake, polyuria, and diarrhea, which cause a steady drain on the chloride and base reserves of the body.

6. Inorganic Phosphate. An increase in the concentration of inorganic phosphorus in the serum is a common finding in advanced renal failure. Values as high as 40 mg. per 100 cc. have been reported, but the common range is from 7 to 15 mg. per 100 cc. This phosphate retention is believed to contribute to some extent to the acidosis of renal failure.

7. Calcium. Some degree of hypocalcemia occurs commonly in advanced renal failure. The decrease in serum calcium concentration appears to be dependent on hypoproteinemia, hyperphosphatemia, or both.

VI. WATER BALANCE

A. WATER

Although the simplest of the food elements, water is probably the most important and is indispensable to life. Water, moreover, is expended constantly in the normal activities of the body, even when intake is interrupted. Deprivation of all water intake, even though no disease is present, leads to impoverishment of the various stores of body water, which produces dehydration and eventually death. *The daily requirement to maintain water balance varies with dietary intake, with environmental conditions and body temperature, and with other factors. It should be large enough, even in the most favorable circumstances, to replace that lost through the kidneys as urine.*

Gamble has estimated that the minimal water expenditure required by normal kidneys is 150 to 900 cc., depending on the quantity and kind of solutes claiming removal. If the intake of protein and of salt is low and of carbohydrate high, 200 cc. may be all that is needed to eliminate all waste products adequately in 24 hours.

Under relatively normal conditions the water requirements may vary within wide limits, but the total amount may not be very great when no excessive losses occur.

The water requirements are greatly increased whenever there are excessive losses. Such losses occur in a wide variety of circumstances. In all these conditions the water contains sodium chloride and occasionally protein. The commonest example is loss of gastrointestinal secretions because of vomiting and diarrhea or as drainage from an intestinal fistula. In extensive tissue trauma, large losses of both water and sodium salts take place.

B. ELECTROLYTE (SALT)

The general term electrolyte refers to the various salts found in the body, including the cations—sodium, potassium, calcium, and magnesium and the anions—chloride, phosphate, bicarbonate, and sulfate. Extracellular fluid, including plasma, contains practically only sodium chloride and bicarbonate, the former comprising about 80 percent. By contrast, the intracellular fluid contains electrolytes which are nearly all potassium and magnesium salts, mostly phosphate, sulfate, and bicarbonate.

While there are no normal mechanisms by which a significant deficiency of sodium chloride alone is produced, large amounts of it are lost in the gastrointestinal secretions that escape during vomiting, in severe diarrhea, and in the drainage from intestinal fistulas. These secretions contain between 0.5 and 0.9 percent sodium chloride.

C. DIFFERENCES BETWEEN WATER AND SALT NEEDS

The requirements for water and salt rest upon fairly different metabolic considerations. In the case of water, the requirements is often acute to meet deficits from vomiting, etc., and also continuous for the excretion of waste products in the urine. Sodium chloride, on the other hand, is urgently required to meet acute deficits, as in the case of water, but is relatively dispensable as far as the daily metabolic needs are concerned.

Circumstances do occur in which unneeded salt actually may prove deleterious. Ordinarily the intake of an excess of sodium chloride, like water, is followed by its immediate excretion by the kidneys. Unlike water, however, salt may not be excreted, particularly when large amounts are given or when renal function is impaired. The extra salt may be so poorly excreted by the kidney that its retention may lead to the accumulation of fluid in the extracellular spaces, thus leading to the development of edema.

Postoperative salt intolerance has been described in considerable detail by Coller and his coworkers. These deleterious effects of saline administration apparently are due to the fact that the kidney may be unable to excrete much sodium chloride for a period of 24 to 48 hours following serious operations, even though the volume of urine is normal. This may be due to the anesthesia or to increased adrenocortical activity, since cortin has been shown to produce sodium retention in the human. When large amounts are given after a severe operation, particularly in malnourished patients, various manifestations may follow owing to accumulation of excess fluid within the body. For this reason, therefore, *water should be given in a solution containing very little sodium chloride for the first few days after extensive surgical procedures.*

D. DEHYDRATION (ANHYDREMIA)

Dehydration affects in varying degrees the two general water compartments of the body, i. e., the extracellular fluid and the intracellular fluid. These are divided anatomically by the semipermeable cell wall of the body tissues. The extracellular fluid is further subdivided into the plasma of the blood and the interstitial fluid, and these are divided anatomically by the more semipermeable capillary wall of the vascular system. Each of these three compartments differs both in chemical composition and in size. Even in moderate dehydration water is lost from each of these two compartments by passage through the dividing barriers. However, intracellular water can be lost in another way—by actual cellular break-down. This process occurs extensively during starvation, when the body must live on its own tissues. But some tissue break-down occurs during water deprivation, even when food intake is adequate.

The first compartment to be affected in dehydration is the blood and interstitial space. As the process continues or becomes severer, the intracellular tissue supplies more and more water.

1. Clinical Manifestations of Dehydration. Dehydration should always be suspected whenever there is a history of water deprivation or of actual loss of gastrointestinal secretions or sweat. Such patients exhibit certain clinical manifestations that may be fairly characteristic. The clinical picture, however, may vary tremendously, depending on the amount and

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type of fluids lost, the rapidity with which they are lost, and the age and general nutritional condition of the patient at the time.

Most of the differences in the clinical picture of simple dehydration depend basically upon whether or not the water deficit is accompanied with a salt deficit, and vice versa. *In the subjects suffering salt loss alone, the following, among other things, are observed: Hemoconcentration, absence of thirst, a fall in extracellular fluid volume, apathy, weakness, anorexia, fainting, and peripheral circulatory failure.* Whenever pure water is given, it fails to relieve the symptoms or correct the dehydration and is merely excreted in the urine. When salt is administered, dramatic improvement follows. This condition is often called acute *salt deficiency,* although the term "water intoxication" is frequently employed.

Nadal, Pedersen, and Maddock noted quite different changes in starved subjects suffering *water deprivation but no induced loss of salt.* There was *no hemoconcentration, great thirst, and no circulatory impairment.* Water alone corrected all the manifestations.

In the mixed type, a good deal of water is lost, together with varying amounts of salt. In such cases the clinical manifestations may partake of both salt loss and water loss. When this is evaluated together with the other factors already mentioned (plus the presence or absence of acidosis or alkalosis), it is easy to see how the clinical manifestations of dehydration may vary from a few insignificant symptoms to alarming circulatory failure.

2. Laboratory Studies. Laboratory studies are often of value in the diagnosis of dehydration. Positive findings include *hemoconcentration,* which can readily be measured by the hematocrit, or just as simply by a rise in the red cell count. This presupposes a normal red cell count before the loss of fluids started. In chonically ill patients preexisting anemia may be masked by hemoconcentration; in such cases a deceptively normal red count will be found. Similarly, dehydration due to water and salt loss is accompanied with an *increase in the concentration of the plasma protein,* provided it was normal before the acute disturbance.

The *urine* in dehydration is usually *scanty, highly concentrated, and of high specific gravity and contains little or no chloride.* The presence of albumin and casts does not necessarily mean the existence of nephritis, since they usually disappear with the correction of the dehydration. *Blood chemical studies* will show a *fall in the chlorides* and may show an *increase in the nonprotein nitrogen* and alterations in the carbon dioxide combining power, indicative of acidosis or alkalosis.

3. Correction of Dehydration. The correction of simple dehydration involves the administration of water containing various amounts of sodium chloride.

a. Dehydration From Water Deprivation Alone. The deficit is due simply to the effects of starvation during which the body stores of water are more or less depleted. A certain amount of salt is lost in the beginning, but the quantity is not great. The correction of this type of dehydration requires a great deal of water with little salt. Because of associated protein deficiency, too much electrolyte is deleterious, and injections of isotonic saline solution (9 gm. per liter) may provoke salt edema in these patients unless measures are taken to build up the lost protein as well.

b. Dehydration From Excessive Loss of Gastrointestinal Secretions and Sweat. These losses follow vomiting, diarrhea, drainage from a fistula, continuous gastric or intestinal drainage, and profuse sweating. Because the fluid lost contains sodium chloride, correction requires water and salt usually in isotonic concentration.

c. Dehydration From Excessive Loss of Gastrointestinal Secretions and Sweat, After Ingestion of Pure Water. This type of dehydration begins the same way as described in subparagraph *b*. However, the patient is able to ingest pure water or is given simple glucose solutions by injection. In either case the water deficit is partly corrected, but the electrolyte deficit persists. Because of this the condition is called acute salt deficiency or water intoxication. Treatment consists in the injection of large amounts of sodium chloride and relatively little water. In actual practice treatment is the same as in subparagraph *b*, inasmuch as injection of excess water of itself is not apt to be deleterious.

E. AMOUNT OF WATER AND ELECTROLYTE NEEDED

Coller and Maddock have devised a formula based on the fall in plasma chlorides to indicate the amount of saline solution required to correct dehydration in surgical patients who have lost a good deal of gastrointestinal secretions.

A simpler though less direct method of determining the amount of fluid required by the dehydrated patient is the bedside response to therapy. Parenteral injections may be considered effective when symptoms are relieved, when hemoconcentration is corrected, and when sufficient urine containing sodium chloride has been secreted. Analysis of the urine for chloride is ordinarily a useful clinical guide of the adequacy of salt replacement, and for this the silver nitrate test is both simple and accurate. Because in dehydration due to loss of salt the body conserves chloride; none will be found in the urine until the deficit is corrected and a little is left over. This conversion of a negative chloride test to a positive one is, ordinarily, good evidence of complete correction. However, kidney function must be normal, lest the absence of chlorides be misinterpreted.

F. DAILY REQUIREMENTS OF WATER AND ELECTROLYTE

The daily water requirement is ordinarily placed at 3 liters, an amount that will meet adequately the metabolic needs of an adult under normal conditions. If tissue protein has been destroyed, replacement will require larger amounts of water, together with protein, magnesium, and potassium, in order to furnish sufficient intracellular water, which comprises 80 percent of the weight of body tissue. *The water needs in infancy and childhood are greater because of the poor concentrating ability of the immature kidney, the greater metabolic requirements due to the larger surface area per unit of body weight, and factors of growth and activity.*

An output of 1 liter or more per day can be assumed to be a good indication of a satisfactory water exchange, particularly when the amount of fluid administered does not exceed 3,000 cc. On the other hand, if the output of urine remains low after a good intake, it does not necessarily mean that more water should be given; such a low output may be due to renal insufficiency or to hypoproteinemia.

In regard to *sodium chloride* it may be stated that under ordinary conditions in a patient who is not severely depleted and with good kidney function, about 5 to 10 gm. is normally excreted daily in the urine. On this basis, the same amount of sodium chloride can safely be added to the fluid intake, i. e., 1 liter of isotonic saline. It is probable that the intake of salt should be greatly reduced, once deficits have been corrected. Because the body is able to conserve salt, withholding sodium chloride simply means that the kidney is spared the necessity of excreting it. This may be useful in the presence of renal impairment, which is not infrequent after operation. Sodium chloride should also be used sparingly in patients with hypoproteinemia and other evidence of malnutrition, because it will tend to aggravate tissue edema and lead to accumulation of fluid in all compartments of the body, even in the lungs. In the absence of actual loss of salts, the fluids injected after operation should consist largely of glucose and amino acids with very little sodium chloride. At most, each liter should contain not more than 3 gm.

The presence of 2 or 3 gm. of sodium chloride in the urine per day is probably a sufficient indication that the electrolyte needs are being met.

Salts other than sodium chloride have been mentioned already. For short periods they do not have a very important function, inasmuch as extracellular fluid consists largely of sodium chloride. On the other hand, intracellular fluid contains electrolytes which are largely potassium and magnesium, and if parenteral fluids and foods are required for the actual rebuilding of tissue, it is likely that these two salts should be looked upon as an essential constituent (with protein) in order that the normal composition of protoplasm can be restored. This situation occurs in surgical patients being prepared for operation with parenteral food because of their inability to ingest any food by mouth.

G. WATER OUTPUT

Water is lost from the body in the feces, urine, and saliva and by the evaporation of water from the skin and lungs. The daily loss through these several channels is given in the following table for an average-sized man at light occupation in a temperate climate.

	Cc
Skin (at average temperature and humidity)	500
Expired air (at average temperature and humidity)	350
Urine	1,500
Feces	150
Total	2,500

The loss in the saliva is negligible in ordinary circumstances but may be considerable in mouth breathers (as a result of evaporation) and in persons addicted to the spitting habit.

The water lost by the skin and lungs varies greatly with the temperature and relative humidity of the atmosphere and with the extent of the muscular exercise indulged in. At ordinary temperatures the loss of water by the skin is not perceived, since the sweat evaporates as quickly as it is formed. This *insensible perspiration,* also includes the evaporation of water from the surface of the body apart from actual sweat secretion. The amount of the

insensible perspiration has the average value given above, but it may be many times this value.

H. EDEMA

Edema consists in the abnormal accumulation of interstitial fluid, either local or general.

The normal interchange of fluid between the vascular compartment and the tissue space depends primarily upon four factors: (1) *The capillary blood pressure* (13 to 35 mm. Hg), lower at the venous end than at the arterial end of the capillary, which tends to drive fluid toward the tissue spaces; (2) *the colloid osmotic pressure* (oncotic pressure) of the blood plasma about 25 mm. Hg), dependent chiefly upon the concentration of plasma albumin, which tends to draw fluid into the vascular compartment, counteracting the effect of the capillary blood pressure; (3) *the relative impermeability of the capillary wall* to protein; and (4) *the lymphatic circulation,* which aids in the removal of fluid from the tissue spaces.

Contributing factors: (*a*) A high intake of sodium if water is available and vice versa; (*b*) low tissue tension, as in the case of the eyelids and genitalia, which favors the accumulation of fluid in those situations. These contributory factors serve merely to increase the tendency to edema in the presence of one or more of the fundamental factors enumerated above.

VII. ACID-BASE BALANCE

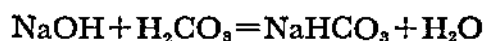
pH is the logarithm of the reciprocal of the hydrogen ion concentration.

The blood plasma is normally slightly alkaline in reaction, the hydrogen ion concentration ranging from pH 7.3 to pH 7.5, averaging 7.35, venous blood (pH 7.32) being slightly more acid than arterial blood. A remarkably efficient mechanism prevents the sudden variations in hydrogen ion concentration which in its absence would occur in the blood and tissue fluids as a result of either the introduction of acid and basic substances from without or their elaboration in the tissues in the course of metabolic activity. This mechanism may be considered under two headings: (1) *Chemical and physiochemical reactions in the blood and tissues* and (2) *excretory processes* by means of which the excess of acid or alkali is eliminated from the body.

A. BUFFER REACTIONS IN BLOOD AND TISSUES

Under normal conditions the hydrogen ion concentration of blood plasma is not materially affected by the addition of relatively large quantities of acid or basic substances. This constancy of reaction is maintained through the operation of certain substances which soak up the excess of hydrogen or hydroxyl ions and which are designated "buffer substances." These buffer systems may be considered under three headings: (1) the bicarbonate system, (2) the phosphate system, and (3) plasma proteins, hemoglobin, and chloride.

1. Bicarbonate system. The bicarbonate system consists of a mixture of carbonic acid (H_2CO_3) and bicarbonate ($BHCO_3$), the most important of the basic elements (B) in this connection being sodium (Na) and potassium (K). The buffer efficiency of this system depends upon the laws governing the reactions of mixtures of weak acids and their alkaline salts.



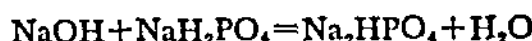
$$NaOH + H_2CO_3 = NaHCO_3 + H_2O$$

The bicarbonate system is particularly effective in maintaining the normal hydrogen ion concentration of the blood plasma, inasmuch as the excess of carbonic acid formed as a result of the interaction of bicarbonate with relatively strong acids formed during metabolic activity in the tissue (hydrochloric, sulfuric, phosphoric, and lactic acids) is removed from the body, as carbon dioxide, through the lungs Likewise, since carbon dioxide is being constantly formed through oxidative processes in the body, any excess of alkali is rapidly transformed into bicarbonate.

Because of these neutralizing properties, the *carbonic acid-bicarbonate system constitutes one of the most important buffer mechanisms of the body, operating particularly in the blood* but to a lesser extent also in the tissue cells; the phosphate system, however, plays a more important role in the latter situation. Because of the fact that the blood bicarbonate represents

a supply of base which is readily available for the neutralization of acids, to it has been applied the term *alkali reserve* of the blood, which, for clinical purposes, may be assumed to be representative of the alkali reserve of the body.

2. Phosphate System. The phosphate system consists of a mixture of monosodium phosphate and disodium phosphate. The hydrogen ion concentration of such a mixture, as in the case of the bicarbonate system, is dependent upon the relative proportion of each of these two substances. The buffer action of a phosphate system is manifested in essentially the same manner as is that of a bicarbonate system.

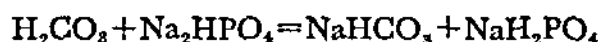


$$NaOH + NaH_2PO_4 = Na_2HPO_4 + H_2O$$

The *phosphate system operates particularly in the tissues* and to a relatively small extent in the blood.

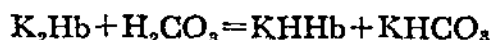
3. Plasma, Proteins, Hemoglobin, and Chlorides. The blood proteins, particularly hemoglobin, albumin, and globulin, play an important part in regulating the hydrogen ion concentration of the blood. The plasma proteins are of much less significance than hemoglobin in this connection.

The mechanisms described are effective in diminishing the disturbing effect of acids stronger than carbonic acid, such as hydrochloric, sulfuric, phosphoric, and lactic acids. However, H_2CO_3, which is the acid formed in largest quantity in the body, cannot be efficiently dealt with by the bicarbonate system.



$$H_2CO_3 + Na_2HPO_4 = NaHCO_3 + NaH_2PO_4$$

The greater part of the base available for the neutralization of the large quantities of carbonic acid entering the blood from the tissues is supplied by hemoglobin and the blood chloride.



$$K_2Hb + H_2CO_3 = KHHb + KHCO_3$$

The diffusion of Cl between the blood plasma and the interior of the red cell is termed the "chloride shift." Van Slyke has estimated that from 84 to 90 percent of the base which is required to deal with H_2CO_3 is supplied directly or indirectly by hemoglobin, the indirect supply being derived from the NaCl of the blood plasma, the buffering action of the hemoglobin, however, being essential for this reaction.

These mechanisms prevent the occurrence of sudden variations in the hydrogen ion concentration of the blood and tissues which in their absence would occur as a result of the entrance or elaboration of acid substances. However, if no other provision were made, the available alkali of the body would soon be used up or rendered unavailable by reason of its combination with these acids. This possibility is obviated by the action of certain excretory processes by means of which the excess acid is removed from the body through various channels.

B. EXCRETORY PROCESSES

The excess acid which must be removed from the body is eliminated chiefly through the lungs, gastrointestinal tract, and kidneys. Any excess of alkali is eliminated largely by the kidneys.

1. Lungs. The lungs are the chief channel of elimination of volatile acids, the most important of which is carbonic acid, the acid formed in largest quantity in the body. The activity of the respiratory center is governed by the hydrogen ion concentration within the cells constituting that center, which is dependent upon the hydrogen ion concentration of the blood and tissue fluid bathing those cells. The respiratory center is remarkably sensitive to very slight variations of the carbon dioxide tension and the pH of the blood.

2. Gastrointestinal Tract. The function of the gastrointestinal tract in regulating the acid-base balance of the body is much less important than that of the lungs or kidneys. During the period of active gastric digestion, large quantities of free hydrochloric acid are secreted into the stomach. This results in a relative increase in the quantity of base in the blood present in the form of bicarbonate, in consequence of which fact the organism attempts to restore the normal equilibrium by the excretion of urine of increased alkalinity. This phenomenon is designated the *alkaline tide.*

Although the part played by the gastrointestinal tract is the maintenance of the normal acid-base balance under physiological conditions is relatively unimportant, in certain pathological conditions affecting the alimentary canal marked alterations in the hydrogen ion concentration of the blood may occur. In this connection, the volume and electrolyte composition of the various digestive fluids are of importance. It is obvious that the continued loss of various digestive fluids can readily lead to a state of marked dehydration.

3. Kidneys. The kidneys play a most important part in the maintenance of the normal acid-base balance. Many fixed acids formed during metabolic processes are eliminated in the urine, chiefly in the form of salts of sodium, potassium, calcium, magnesium, and ammonia (chlorides, phosphates, carbonates, and sulfates). In addition, in the kidneys, the disodium phosphate of the blood plasma (Na_2HPO_3) is transformed into the acid phosphate (NaH_2PO_4), which contributes largely to the normal acidity of the urine. This phenomenon aids materially in conserving the available base of the blood and in counteracting any tendency toward an increase in the hydrogen ion concentration of the plasma. In normal circumstances the kidneys constitute an extremely delicate mechanism for the elimination of excessive quantities of fixed acids and bases from the body, operating in a manner comparable in efficiency to the action of the respiratory mechanism in eliminating excess quantities of carbonic acid.

Formation of *ammonia* in the kidneys is another extremely important factor in the preservation of the normal acid-base balance. Ammonia, formed in the kidney from amino acids, combines with these acid radicals and thus conserves the available base supply of the body. The ammonia-forming mechanism is stimulated by the necessity for the elimination of increased quantities of acids other than carbonic and phosphoric, and, therefore, the urinary ammonia is increased after the ingestion or formation in the body of increased amounts of acid substances.

C. ACIDOSIS

The term "acidosis" is applied to the condition resulting from the formation of absorption of acids at a rate exceeding that of their neutralization or elimination. An increase in the hydrogen ion concentration of the blood (acidosis) may be caused by either an increase in the concentration of H_2CO_3 or a decrease in the concentration of $BHCO_3$. If these changes are of such magnitude that the hydrogen ion concentration rises above the upper limit of normal (pH below 7.3) the condition is one of *uncompensated acidosis.* If in such circumstances the hydrogen ion concentration of the blood is maintained below the upper limit of normal (pH above 7.3), the organism is in a state of *compensated acidosis.* The clinical conditions in which a state of acidosis is commonly observed will be considered under two headings:

(1) *Those associated with a primary increase in the concentration of H_2CO_3 in the blood* and (2) *those associated with a primary decrease in blood bicarbonate (alkali reserve).*

1. Primary Carbonic Acid Excess. Increase in the carbonic acid content (carbon dioxide tension) of the blood may occur in one of two general ways: (1) Rebreathing or (2) conditions in which the elimination of carbon dioxide through the lungs is retarded.

Compensatory Mechanisms

(1) Increased ventilation.
(2) Increase in alkali reserve.
(3) Increased ammonia formation.
(4) Increased urinary acidity.

2. Primary Alkali Deficit. Primary alkali deficit is the commonest cause of acidosis occurring in clinical conditions:

Diabetes mellitus.
Renal failure.
Starvation.
Anesthesia.
Dehydration.
Ingestion of acids.
Pregnancy and toxemias of pregnancy.

Compensatory Mechanisms

(1) Increased pulmonary ventilation.
(2) Increased ammonia formation.
(3) Increased acid excretion.

D. ALKALOSIS

Alkalosis is a state in which either excessive amounts of acid are lost from the body without a comparable loss of base or alkali, or alkali is formed in or supplied to the body at a rate exceeding that of its neutralization or elimination. In terms of the bicarbonate system, alkalosis may result from either a primary decrease in the carbonic acid of the blood or a primary increase in blood bicarbonate (alkali reserve). A primary change in one of these factors is almost invariably associated with or followed by a secondary change in the same direction in the other factor, the hydrogen ion concentration of the blood in these circumstances being but little affected,

the condition being one of *compensated alkalosis.* As the metabolic error progresses, however, the compensatory secondary change becomes insufficient to maintain the normal balance and the hydrogen ion concentration of the blood diminishes below the lower limit of normal (pH above 7.5), constituting a state of *uncompensated alkalosis.*

1. Primary Carbonic Acid Deficit. Excessive quantities of carbon dioxide may be washed out of the blood by hyperventilation of the pulmonary alveoli. Clinically, it is observed in the following conditions:

Hysteria.
Fever.
High external temperatures.
Anoxic anoxemia.
Encephalitis.

Compensatory Mechanisms

(1) Excretion of alkali.
(2) Decreased acid elimination.
(3) Decreased urinary ammonia.
(4) Retention of acid metabolic products.

2. Primary Alkali Excess. Primary alkali excess or increase in the alkali reserve is the most frequent cause of clinically observed alkalosis. It occurs in the following conditions:

Excessive loss of HCl from the stomach.
Alkali administration.
Roentgen ray and ultraviolet irradiation and radium therapy.

A decrease in the hydrogen ion concentration of the blood plasma (increased pH) has been observed following deep X-ray therapy, radium therapy, and prolonged exposure to ultraviolet rays.

Compensatory Mechanisms

(1) Increased alkali excretion.
(2) Decreased acid excretion.
(3) Decreased ammonia formation.
(4) Retention of acid metabolic products.
(5) Decreased pulmonary ventilation.

E. ALKALI RESERVE OF BLOOD

For clinical purposes it may be assumed that changes in the alkali reserve of the body are reflected in the bicarbonate concentration (alkali reserve) of the blood.

1. Carbon Dioxide Capacity of Plasma. The carbon dioxide capacity or carbon dioxide combining power of the blood plasma is expressed as the number of cubic centimeters of carbon dioxide which can be bound as bicarbonate by 100 cc. of blood plasma at 0° C. and 760 mm. Hg pressure. Inasmuch as the ability of the plasma to combine with carbon dioxide to form bicarbonate depends, in the final analysis, upon the quantity of available alkali present (alkali reserve), the determination of the carbon dioxide combining power or capacity of the blood plasma is a direct measure of the alkali reserve. The normal values for adults range from 50 to 60 cc. of carbon dioxide bound as bicarbonate by 100 cc. of blood plasma (55 to 60 volumes percent). The normal values for infants are about 10 volumes

percent lower than those for adults. Decrease or increase in the carbon dioxide combining power is indicative of a corresponding change in the alkali reserve.

The determination of the carbon dioxide combining power of the blood plasma is perhaps the most valuable single means of estimating the degree of acidosis or alkalosis in most instances.

2. Treatment of Acidosis and Alkalosis. In most cases of acidosis or alkalosis, spontaneous correction follows treatment of the dehydration by the injection of sufficient saline solution or correction of shock by plasma or blood transfusions. Restoration of the acid-base balance takes place by the simple mechanism of dilution of the viscid blood, aided by the action of the kidney in removing excess acid or base.

In certain cases these relatively simple measures will fail or be inadequate, and appropriate neutralizing solutions may have to be injected directly into the blood stream. Such treatment is indicated oftener in acidosis than in alkalosis, particularly since acidosis is more likely to be associated with extensive injury producing circulatory impairment and with severe post-operative states. Moreover, renal function is apt to be impaired after operation or injury, thus adding to the necessity for the use of such a direct neutralizing mechanism. Sodium bicarbonate is well known, and solutions of it have long been employed in the treatment of acidosis. More recently sodium lactate has been described by Hartmann. Sodium lactate has the following advantages over bicarbonate: It is easier to prepare, is more stable, and furnishes calories as well as alkali. Sodium lactate is metabolized rapidly after intravenous injection, forming bicarbonate and glucose, thus giving an almost immediate compensation for acidosis long before the kidney is able to do so.

The dose of alkali needed will obviously vary with the severity of the case. If it is possible to measure the carbon dioxide combining power of the blood, an accurate estimation of the degree of acidosis can be made. The following doses for the use of bicarbonate and lactate have been recommended, the normal carbon dioxide content of the plasma being placed at 60 volumes percent.

For each volume percent that the plasma carbon dioxide is less than 55 volumes in a 60-kg. man *one* of the following is given:

(1) 40 cc. of 4 percent $NaHCO_3$ intravenously.
(2) 125 cc. of 1.3 percent (isotonic) [illegible]
(3) 125 cc. of 1.75 percent (isoton [illegible]

In contrast to acidosis, the injection of [illegible] is very seldom indicated. The reason simply is that most patients with alkalosis respond satisfactorily to injections of isotonic saline or 5 to 10 percent glucose in saline. On rare occasions, desperately ill patients with alkalosis do not respond to the usual measures and may require more heroic therapy. In such a case, one of the following two solutions has been used: A dilute solution of hydrochloric acid itself and a solution of ammonium chloride. Perhaps a safer method for the correction of alkalosis might be the injection of acid solutions of amino acids.

VIII. SHOCK

A. DEFINITION

Shock is a disturbance of fluid balance resulting in a peripheral circulatory deficiency which is manifested by a decreased volume of blood, reduced volume flow, hemoconcentration, and renal functional deficiency.

B. SHOCK VERSUS EFFECTS OF HEMORRHAGES

1. Features Identical in Shock and Hemorrhage

a. Sympathoadrenal activity.
- (1) Stimulation of myocardium.
  - (a) Strong rapid pulse in early stages.
- (2) Peripheral vasoconstriction.
  - (a) Reduced volume flow.
  - (b) Peripheral ischemia, pallor.
  - (c) Loss of tissue turgor.
- (3) Discharge of reservoir blood into systemic circulation.
  - (a) Contraction of spleen.
- (4) Increased blood sugar.
- (5) Dilatation of pupils, often perspiration.

b. Low basal metabolism.
- (1) Declining temperature.

c. Decreased alkaline reserve.

d. Increased respiratory rate, thirst.

e. Low arterial blood pressure (in late stages).

f. Death due to inadequate circulatory function.

2. Contrasted Features

Items	*Shock*	*Hemorrhage*
Endothelium	Permeable to colloids	Impermeable
Flow of lymph	Increased	Decreased
Tissue fluid	Increased	Decreased
Fluid balance	Disturbed	Undisturbed
Absorption	Impaired	Unimpaired
Vomiting	Persistent	Absent
Diarrhea	Frequent	Absent
Saline solutions, intravenous	Ineffective	Often effective
Renal		
Excretion	Deficient	Unimpaired
Urine	Concentrated, low volume albumin, erythrocytes, bile, debris	No characteristic changes

Items	*Shock*	*Hemorrhage*
Blood		
Coagulation time	Lengthened	Shortened
Concentration	Increased	Decreased
Nonprotein nitrogen	Increased	Decreased
Potassium	Increased	Terminal increase
Plasma chlorides	Decreased	Increased
Necropsy findings		
Edema of soft tissues	Characteristic	Absent
Serous effusions	Present	Absent
Capillariovenous congestion	Characteristic	Absent
Petechiae	Characteristic	Absent
Visceral ischemia	Absent	Present
Organ weight	Increased	Decreased
Gastrointestinal tract	Dilated, atonic	Contracted
Parenchymal necroses	Present	Absent

Pathologic Changes in the Viscera After Death by Shock. Consist in capillary atony, hyperemia, statsia, edema, and ecchymoses in the lungs, mucosae, serous surfaces, liver, and kidneys.

C. TRAUMATIC SHOCK

The attention of surgeons is focused upon shock following trauma. Many recognize that at least three mechanisms may cause low blood pressure after injury. One of these, *primary or neurogenic shock,* is a neurovascular reaction like that of syncope or fainting. This develops promptly after injury and is usually transient unless accompanied with extensive trauma or hemorrhage. Occasionally, primary shock may merge gradually into secondary shock without an interval of partial recovery. Hemoconcentration is not present in primary or neurogenic shock.

The *effects of hemorrhage* are an obvious cause for low blood pressure. This may develop promptly from voluminous hemorrhage or gradually from slow or repeated small hemorrhages. The clinical signs of hemorrhage are like those of secondary shock, but it has been shown that they differ in other important particulars. Hemorrhage is followed by a rapid dilution of the blood which, in otherwise normal subjects, is proportional to the volume of blood lost. Low blood pressure occurring shortly after trauma is due chiefly to neurovascular and hemorrhagic effects.

The third mechanism results from deranged capillary function. Products of tissue autolysis or of infection, absorbed from damaged tissues, produce systemic effects like those of capillary poisons. Consequent leakage of fluid lowers the blood volume and causes hemoconcentration. Decreased blood volume, combined with increased volume capacity of the capillary bed, causes circulatory deficiency. This mechanism requires time for development—it is never seen immediately after injury, hence it is called *delayed or secondary shock.*

The same mechanisms that operate in shock also operate in severe infections, metabolic intoxications, abdominal emergencies, and effects of various poisons.

1. Circulatory Dynamics. Moon states that any kind of injury to the endothelium increases its permeability to the plasma colloids.

Permeability of capillary endothelium lowers both the actual and the effective blood volume. Leakage of plasma into the tissue spaces reduces the *actual* blood volume and causes hemoconcentration, whereas sequestration of blood by stasis in dilated capillaries and venules reduces the *effective* blood volume. This combination leads to a disparity between the volume of blood and the volume capacity of the vascular bed. Such a disparity produces a circulatory deficiency superficially resembling that resulting from hemorrhages. Physiological reactions compensate for minor degrees of such a deficiency. Activity of the sympathoadrenal system causes arterial constriction, stimulates cardiac function, and causes the spleen to contract and discharge its reserve of blood into the circulation. Selective distribution of blood favors the vital organs at the expense of nonvital parts. Peripheral circulation is reduced, and the external parts become pale, cold, and almost pulseless.

So long as this compensation is effective there is no marked decline in the arterial blood pressure, but the latter is maintained at the expense of the volume flow. Stagnation of the circulation in the dilated capillaries reduces the amount of venous blood returned to the heart. This lessens the cardiac output and decreases further the volume flow. A reduced delivery of oxygen to the tissues follows, with accompanying anoxia, which in itself causes further relaxation and permeability of the capillary endothelium. This feature introduces a self-perpetuating factor into the mechanism, which causes it to progress in a vicious circle. When finally the compensatory reactions are no longer adequate, the blood pressure declines progressively and the complete syndrome of shock is manifested clinically.

2. Three Major Physiological Disturbances Accompany Shock

a. Fluid Imbalance. Several forces are concerned with movement of fluid between the blood and the tissues in either direction. Chief among these are capillary blood pressure and the osmotic attraction of the plasma colloids. The operation of these forces requires the presence of a semipermeable membrane—the endothelium. Immediately as the endothelium becomes permeable to colloids, the force known as osmosis ceases to act and the vital mechanism of fluid balance can no longer function. Endothelium so permeable that it allows plasma to escape freely is incapable of maintaining physiological relationships between the intra- and extravascular fluids.

One function of fluid balance maintains the volume and composition of the blood at normal levels. When fluid balance is deranged, as by abnormal permeability of capillary endothelium, fluid leaks out into the tissue spaces. This reduces the volume of the blood and increases the numerical count of the erythrocytes—a condition known as hemoconcentration.

It has been shown that *hemoconcentration is the earliest detectable sign of secondary shock and a valuable index of its degree or severity.*

b. Imbalance of Electrolytes It has been shown that the outer surface of normal cells functions as a semipermeable membrane and that some vital property of living protoplasm maintains a chemical concentration *within* the cell which differs markedly from that of the *external fluid.* This property is decreased by lack of oxygen or by any kind of damage to the cell; the property is lost entirely as the cell dies.

The cellular and extracellular fluids differ markedly in their content of potassium and of sodium.

The *effects of anoxia* or of deleterious agents render the protoplasm incapable of maintaining these differences in ionic concentrations. Immediately there is a movement of ions from the region of the higher to that of the lower concentration, which tends to equalize them. Obviously this will increase markedly the potassium content of the plasma and decrease its content of sodium.

c. Renal Dysfunction. In shock from diverse causes this is evidenced by oliguria or anuria; by a progressive accumulation of nitrogenous wastes in the blood; and by casts, debris, albumin, and other abnormal findings in the urine. Renal deficiency becomes prominent when patients survive for several days in a state of sublethal shock. It frequently happens in such cases that defective renal function comes to dominate the clinical picture. This is exemplified in *crush injuries*, in nonfatal shock from trauma or from burns, intestinal obstruction, metabolic intoxication as in diabetes, icterus gravis, toxemia complicating pregnancy, anaphylactic reactions, transfusions with imcompatible blood, poisoning with various drugs, and in severe infections.

3. Clinical Implications and Treatment. The successful management of shock requires primarily that the conditions which cause it shall be obviated or removed.

In the treatment of shock, the first essential is an *accurate differential diagnosis between three conditions* which commonly result from wounds and which present similar clinical features. These are:

(*a*) *Primary or initial shock*, (*b*) the *effects of hemorrhages*, and (*c*) *true shock*, otherwise known as *secondary or delayed shock*.

Hemoconcentration is most valuable for differentiation. It may be shown either by counts of the red blood cells, by hemoglobin readings, by hematocrit, or by the specific gravity of the whole blood.

Primary or initial shock is essentially similar to fainting or syncope. Primary shock is not associated with capillary atony or endothelial permeability; hence it does not produce concentration of the blood. The lapse of time between the injury and the circulatory disturbance and the presence or absence of hemoconcentration are valuable points of distinction between primary and secondary shock.

Severe hemorrhages will cause clinical signs like those of secondary shock. They may be differentiated by the fact that *hemodilution occurs immediately* after hemorrhages, and the degree of dilution is proportional to the amount of blood lost. If the hemoglobin and red blood cells are not reduced below 50 percent, an otherwise healthy person will recover spontaneously. Fluids given by mouth or intravenously, or transfusions of blood or of plasma, will hasten recovery. If the hemoglobin is much below 50 percent, a transfusion of blood should be given.

True or secondary shock requires several hours for development. It is seldom seen within 4 hours, except following abdominal or cranial injuries.

The incipient stage of shock may be detected by the presence of moderate hemoconcentration, 10 to 20 percent, even before any evidence of circulatory deficiency is manifested clinically. This finding will serve to distinguish it from either primary shock or from the effects of hemorrhage.

Morphine is dangerous when given in full doses because it inhibits respiration and thereby increases anoxia which is a major factor in this condition. Sufficient morphine should be given to allay pain and apprehension, but amounts sufficient to lower the respiratory rate will accelerate the development of shock.

Recent evidence, both experimental and clinical, indicates that the use of *heat* in the treatment of shock causes further circulatory deficiency and that the results are detrimental.

Lack of *oxygen* accelerates the development and progress of shock. The inhalation of oxygen aids in counteracting this and in preventing irreparable damage. It raises metabolic activity and tends to interrupt the action of the vicious circle even after shock has been initiated.

One function of the *adrenal cortex hormone* is to maintain the normal impermeability of the endothelium. There is significant evidence, both experimental and clinical, that this substance is distinctly beneficial in the prevention and in the treatment of shock.

After serious hemorrhages, *transfusions of whole blood* provide the ideal remedy. However, in shock accompanied with hemoconcentration, whole blood is not so suitable; it does not relieve the hemoconcentration which, because of viscosity, tends to impede the circulation through the capillaries. The patient does not lack erythrocytes, but he sorely needs fluid to restore the blood to its normal composition and volume. These considerations indicate clearly that the ideal replacement fluid is either *human plasma or serum.*

Concentrated plasma or serum given intravenously raises the colloidal osmotic pressure of the blood and thereby draws fluid from the tissues into the vascular system. This accomplishes several desirable results: It increases directly the total blood volume; it relieves the hemoconcentration, reduces the viscosity of the blood, and restores fluid balance; it tends to reduce the edema of soft tissues; it also relieves the hypoproteinemia which often is a notable feature. These effects increase the circulatory efficiency and the delivery of oxygen to the tissues. The relief of anoxia removes a most important factor from the vicious circle by which the deficiency progresses.

D. RECENT ADVANCES IN PATHOLOGIC PHYSIOLOGY OF SHOCK

1. Blood Volume. Richards has summarized the findings of various investigators in the following statement: "The essential finding in all appeared to be an inadequate venous return of blood to the heart with diminished cardiac output. The anatomical factor immediately responsible for this, in most instances, was a deficit in circulating blood volume." The extent of the reduction in blood volume is directly proportional to the magnitude of the injuries. Ebert and Stead have reported their clinical observations on the shock which is recognized to follow certain severe infections. They found that the blood volume might be normal even though other measurements of the circulation indicated a profound peripheral vascular collapse. In the presence of severe infection or prolonged hypotension, some factor other than reduced blood volume must be considered in order to explain the circulatory failure.

2. Capillary Permeability. Many of the former concepts of shock postulated a generalized increase in capillary permeability as the mechanism for the loss of plasma from the circulation. This supposed change in permeability was considered to be due to the action of toxins absorbed from traumatized areas or to result from anoxia due to reduced circulation. By some, increased capillary permeability was considered to be one of the initiating factors in shock, and by many it was thought of at least as a contributing or sustaining agency. Direct studies of capillary permeability by numerous investigators have generally failed to demonstrate loss of plasma from the blood stream other than into the region of injury.

Fine and Seligman, by the use of plasma proteins tagged with radioactive isotopes, examined the capillary leakage hypothesis in hemorrhagic, tourniquet, and burn shock. They found that the tagged plasma proteins escaped in considerable quantities into the traumatized areas but not into regions remote from trauma. Only in the late stages of shock and after the administration of large quantities of saline was there evidence of the passage of significant amounts of plasma into nontraumatized areas.

3. Question of Infection. The possibility that peripheral circulatory collapse which could not be accounted for on the basis of the amount of fluid lost into the area of injury might be due to the development of toxins from infection in the traumatized muscles must be considered.

4. Failure of Local Fluid Loss to Account for Shock. The volume of fluid lost into the region of trauma is frequently not sufficient to account for the decrease in plasma volume, and there is frequently no correlation between the amount of local loss and the survival or death of the animal.

5. Failure of Replacement Therapy to Prevent Shock. The fact that replacement therapy is not always effective in preventing shock is another indication that simple loss of plasma or blood volume alone is not the sole explanation. Ebert and Stead have shown that when peripheral circulatory collapse is due to infection it will not respond to increasing the blood volume but only to controlling the infection. This failure of the administration of blood to combat shock which is due to infection does not mean that restoration of the depleted blood volume which is simultaneously present will not be of help.

6. Failure of Replacement Therapy in Irreversible Hemorrhagic Shock. The inability of replacement therapy to prevent death from hemorrhagic shock, if the circulation has been seriously depressed for a considerable time, is a well-known fact. Wiggers and Ingraham have differentiated three major conditions which may develop from uncomplicated hemorrhage of variable duration and intensity: Simple hemorrhagic hypotension, impending shock state, and irreversible shock. Frank, Seligman, and Fine came to the conclusion that "advanced shock constitutes a state of progressive deterioration which is not amenable to the types of therapy now available, probably because fundamental biochemical changes have developed as a result of prolonged deficiency of capillary flow. These changes may result from injury predominantly involving one vital organ, such as the liver, or from widespread cellular damage."

7. Metabolic Changes. Stead and Warren have brought out clearly the fact that the "generalized failure in cellular metabolism is a frequent cause of the shock syndrome," however this failure be produced. Search for the significant disturbances have not as yet provided a clear answer as to the nature of the process involved, but there have been numerous suggestive studies.

Considerable interest has been shown in the *enzymatic processes* in shock.

The value of sodium succinate as a supplement to the use of dog plasma albumin in the treatment of shock due to the application of a tourniquet was reported by Mylon, Winternitz, and de Süto-Nagy. However, sodium succinate was found by Hechter, Bergman, and Prinzmetal to be no more effective in the treatment of shock due to burns than was sodium chloride.

Chemical changes in muscle due to anoxia and injury have also been of interest. There is the possibility that the products of tissue metabolism may contribute to the development of acidosis. This acidosis has long been recognized as a constant accompaniment of shock. The renal shut-down which Cournand and his associates have demonstrated would necessarily hasten the development of acidosis through failure to maintain the acid-base balance. Wiggers and Ingraham have shown that acidosis is a factor which contributes to the irreversibility in hemorrhagic shock.

Certain other metabolic changes have been noted, such as the increased fragility of the red blood cells. Tagnon, Levenson, Davidson, and Taylor have recently reported fibrinolysis in both clinical and experimental shock. It was suggested that the fibrinolysins might come from the break-down of body cells.

E. CONCLUSIONS

Numerous mechanisms are involved in the production of shock. The simplest, and probably the commonest, is the failure of return flow of blood to the right heart with consequent reduction in cardiac output. This condition, which usually results from hemorrhage or from the loss of blood or plasma into the area of injury, is readily and understandably amenable to replacement therapy, provided that the circulatory depression is of short duration. If the contrary is true, irreversible changes in the metabolism of cells throughout the body may be produced because of prolonged circulatory insufficiency.

In a second large group of cases, the peripheral circulatory collapse results from metabolic disturbances in cells throughout the body, such as that seen in overwhelming infections. The irreversible shock associated with prolonged circulatory insufficiency probably is essentially similar in its underlying mechanisms. Physiological and pathological studies on various enzymatic functions suggest that the liver is intimately concerned with the development of this stage of irreversibility.

IX. BLOOD SUBSTITUTES

A. STORED CITRATED BLOOD

When whole citrated blood is refrigerated under optimal conditions, there is a gradual drop in the total erythrocyte count, which reaches from one to one and one-half million red cells per cubic millimeter in about 30 days. The longer the blood is stored, the shorter will be the survival time of the red cells in vivo following transfusion. On this basis, *blood stored longer than 7 days is relatively inefficacious* for the primary purposes of transfusion. The *total leukocyte count* falls 50 percent during the first 24 hours, and by the tenth day no intact cells remain. The most fragile are the polymorphonuclear leukocytes. There is a marked increase in *erythrocyte fragility,* which may be controlled to some extent by the type of buffered diluent which is used, dextrose citrate buffer solution apparently being the most satisfactory. The *prothrombin* falls rapidly to a therapeutically ineffective level, and thereafter a gradual loss continues. *Potassium* diffuses from the red cells into the plasma at an initial rapid rate, and then more slowly until equilibrium has been established. As the potassium content of the plasma rises, the *sodium* content decreases, probably because of diffusion into the red cells. There is a gradual loss in total *effective bactericidal* activity, which becomes most marked after from 7 to 21 days of storage. It would therefore appear that while stored blood is relatively effective in the treatment of *acute hemorrhage,* it is inferior in the treatment of acute and chronic infections, hemorrhagic states, and the anemias. When used for these purposes, the storage period should not exceed 72 hours.

Taylor and Waters have outlined the properties of a transfusion fluid requisite to the restoration and maintenance of circulating blood volume as follows:

(a) The molecule of the dissolved substance must be of such a size that the fluid will not leave the vessels too freely.

(b) The solution must exert an osmotic pressure and possess a viscosity approaching as closely as possible that of whole blood; these qualifications depend upon molecular size and shape.

(c) It should be as nearly as possible isotonic with the contents of the erythrocytes.

(d) It must, of course, be nonantigenic and innocuous in every respect. In addition, it should be readily available, preferably cheap, and capable of being quickly and easily prepared for intravenous administration.

B. ACACIA

Although acacia was shown to have a limited effectiveness in the treatment of shock, unfavorable reactions and an understanding of its fate within the body have largely discouraged its use. The principal objections to acacia are that it has been shown to possess a *definite antigenicity;* that

the material is *fixed and stored in the liver;* and that the *plasma proteins may be depressed* to very low levels, particularly the fibrinogen, which causes prolongation of the bleeding time. Furthermore, acacia *fails to supply the body with a source of protein* which is so urgently needed in the treatment of hemorrhage and shock.

C. PECTIN

Pectin is derived from citrus fruits. It is a colloidal carbohydrate of high molecular weight, which, together with the mother substance protopectin, is found in plant cells in combination with cellulose, from which the pectin can be separated by hydrolysis.

The material is prepared for intravenous administration by the addition of electrolytes and adjustment of the pH to 6.5 with phosphate buffer solution. The mixture is then autoclaved and adjusted to a final pH of 7.2. A solution containing 0.5 percent of pure pectin has approximately the same viscosity and osmotic pressure as the blood.

Pectin appears to be *nontoxic* and, when injected intravenously, is eliminated by the kidneys in approximately 72 hours. Preliminary experimental and clinical studies indicate that it is *nonantigenic* and is of value in the treatment of shock in human beings, but the limitations of this form of treatment have not yet been fully ascertained.

D. ALBUMIN FRACTION

As the result of the brilliant work of Cohn, much interest has been aroused in the use of the *albumin fraction* of human plasma in the treatment of traumatic shock. Plasma consists largely of water, each liter containing about 900 cc. Next to water, the main constituents of plasma are the proteins with molecules which are extremely large and of high molecular weight. The *functions* of these *proteins* are diverse, having to do with the *clotting of the blood, immunity from disease,* and *maintenance of osmotic pressure* of the blood and, hence, the *water balance of the body;* some are hormones and enzymes, of which the functions have not yet been determined. It is possible to separate this complex series of proteins by precipitation under varying conditions of temperature and hydrogen ion concentration, so that separate fractions consisting of fibrinogen, gamma globulins, prothrombin, alpha and beta globulins, and the serum albumins may be obtained.

The *albumin fraction* makes up approximately *65 percent* of the proteins of the blood and exerts *85 percent* of the osmotic pressure provided by normal human plasma. By definition, the albumins are water soluble; *100 cc. of buffered saline solution which contains 25 gm. of human alubmin exerts approximately the same colloidal osmotic pressure as 1000 cc. of whole blood or 500 cc. of normal plasma.*

Preliminary studies have indicated that *albumin is effective in the treatment of traumatic shock* in human beings; but, if dehydration is also present, sufficient additional fluid must be administered to attain a positive fluid balance. The amount of blood required to produce a unit containing 25 gm. of albumin in 100 cc. is approximately three times that required for a unit (250 cc.) of plasma containing approximately 17 gm. of osmotically active protein.

E. BOVINE PLASMA

Attempts have been made by several investigators to use *bovine plasm* as a substitute for human plasma or whole blood, but the procedure has bee found impractical because of the marked reactions which have occurred i a considerable percentage of the cases.

The *major drawback* to the use of bovine plasma lies in the *sensitizatio of the patient to beef protein,* which is largely brought about by the gamm globulins.

F. HUMAN PLASMA

Plasma has been found to be more effective than whole blood in the treat ment of:

1. *Shock,* unless accompanied with extreme blood loss.
2. *Severe infections,* as a means of supplying specific and nonspecific anti bodies.
3. Various conditions associated with *hypoproteinemia,* such as nephrosi chronic infections, repeated paracenteses, severe burns, ulcerative coliti and certain liver diseases.
4. Many *blood dyscrasias,* especially those characterized by hemolyti tendencies or fibrinogen deficiency.
5. *Cerebral edema* accompanying various injuries and toxemias.
6. *Acute hemorrhage* in emergencies until whole blood becomes availabl

Plasma is available in three basic physical states, each of which has its ad vantages as well as some disadvantages with respect to the particular ci cumstances in which it is to be used. *The first is plasma which has bee stored under refrigeration as a simple liquid;* this form has proved usef in hospitals which operate blood banks and hence have a relatively low co and readily available supply of raw material. Liquid plasma, prepared b means of a closed system and scrupulous aseptic technic, is both safe an satisfactory over limited periods.

While liquid plasma has been used successfully in the treatment of trau matic shock after shipment without refrigeration over long distances, th statement should not be interpreted as recommending the use of plasm for general purposes after long periods of unrefrigerated storage. Eve under the optimal conditions of storage at from 5° to 10° C., a progressiv loss of prothrombin, complement, and other liable constituents occurs, an this loss may be of considerable importance in the treatment of certain typ of cases. Furthermore, the precipitation of fibrin, though inevitable, slowest in this temperature range, above which its formation is proportio ately more rapid.

A second manner in which plasma may be preserved is in the frozen stat So long as the plasma can be maintained at a temperature of from −15° t −20° C., it can be preserved indefinitely with little deterioration of any c its components. Plasma stored in this manner must be thawed quickly a 37° C. in order to prevent the precipitation of fibrin, which occurs the product is thawed slowly. After thawing, however, it may be store between 5° and 10° C. for from 6 to 8 weeks, with only a relatively sligh loss of its major labile constituents. The main disadvantages of froze plasma are that constant low temperature refrigeration must be maintaine

and proper thawing requires from 20 to 25 minutes, with the result that the material is not available for instant use in an emergency unless it has been previously thawed and stored in the liquid state.

In an attempt to find a method of more permanently preserving plasma without deterioration of its labile constituents, many different processes have been devised. All have the common purpose of removing the moisture content of the plasma without denaturing or otherwise causing any alteration of the plasma proteins.

Of the many procedures which have been studied, one of the most effective, since it results in no detectable alteration in the plasma solids, is the method of desiccating the plasma *from the frozen state under high vacuum.* This method of rapid freezing and dehydration under high vacuum from the frozen state (which has been referred to as the *lyophile technic* has been successfully applied to the preservation of a wide variety of therapeutic agents derived from living sources.

It has been noted that the protein patterns for the lyophilized plasma differ little from that of the fresh liquid control, while that which was simply dried at 37° C. showed wide variation. In 1935, Flosdorf and Mudd reported that the content of antibodies and complement in serum which is rapidly frozen and dehydrated from the frozen state under high vacuum suffers no detectable loss in processing and, furthermore, that the rate of subsequent deterioration is reduced to a small fraction of that which occurs in the liquid state.

There seems to be no question that, as far as the *prothrombin* content of liquid plasma is concerned, deterioration occurs slowly at low temperatures but is very rapid at 37° C. Little or no loss appears to occur in material which is kept frozen.

Plasma, regardless of the method of preservation, possesses certain definite practical advantages over other blood substitutes. Plasma may be defined as that fluid portion obtained from whole blood containing an anticoagulant such as sodium citrate, after removal of the red and white corpuscles by centrifuging or sedimentation. It contains all the proteins, i. e., albumin, globulins, and fibrinogen, which normally occur in the fluid portion of the circulating blood. Serum differs from plasma in that it is obtained from coagulated blood and, therefore, does not contain fibrinogen. At the present time, medical thought is somewhat divided with respect to the relative efficacy of serum and plasma, but a review of the literature indicates that the reactions from serum significantly exceed those following the administration of plasma. However, from a practical standpoint, serum is easier to prepare than plasma, since it can be rendered sterile by candle filtration, whereas plasma cannot. It has also been pointed out that the reactions to serum are minimal when the material used has been allowed to age in contact with the clot, rather than drawn off immediately.

Because of the high osmotic pressure exerted by the plasma proteins, plasma does not diffuse from the circulation as readily as do crystalloid solutions; consequently, plasma is far more effective in restoring and maintaining the circulating blood volume.

One of the most practical advantages of pooled human plasma is that it may be used immediately when required without preliminary delay due to typing and cross matching. *These procedures are unnecessary for two reasons: First,* the agglutinin titer of the pooled plasma is extremely low. When a pool consists of the plasma obtained from 25 to 50 bleedings the agglutinin titer against all major blood groups is usually in the neighborhood of 1: 2 and rarely above 1: 4. Plasma of this agglutinin titer obviously cannot cause a significant degree of agglutination of the recipient's red cells regardless of the type. *Second,* no erythrocytes are present in the plasma which might be agglutinated by the potentially incompatible serum of the recipient.

Confusion appears to exist with respect to the occurrence of the so-called anti-Rh factor in pooled plasma. Actually when one considers the underlying factors which would necessarily be involved for the presence of anti-Rh isoagglutinins in pooled plasma it is evident that the chances of this occurrence are remote. The chances that this factor would cause a reaction if it were present are still more remote, since, first, it would have to be present in significant titer, and, second, it would have to be administered to a reactive patient, i. e., a pregnant woman, who had become sensitized to the Rh-positive blood of her fetus, which in itself is not common. Furthermore, the plasma would have to be taken from a pool containing a significant proportion of blood from a parturient woman—a possibility in hospital operated banks; but this would be unlikely with regard to the commercial desiccated form of plasma, since with few exceptions the professional donors from whom the blood is obtained are males.

An advantage of plasma over other blood substitutes is that it may be quickly and simply administered, under adverse conditions if necessary, as no complicated apparatus or assistance is required. Plasma is safe, as large amounts of citrated plasma have been rapidly and repeatedly administered without causing untoward reactions.

Another therapeutically important fact is that *plasma,* in contradistinction to whole blood, *does not further increase the hemoconcentration which invariably accompanies shock and severe burns.*

Plasma prepared retains its therapeutic value and remains stable without refrigeration for at least 5 years. With the exception of the formed elements, each unit is equivalent to approximately 500 cc. of whole blood. Plasma prepared in this manner has the further advantage that it may be restored for use in concentrated form.

One of the greatest indications for the administration of plasma is shock. The essential aim in the treatment of shock—regardless of whether the condition is hematogenic, neurogenic, or vasogenic in origin—is the restoration of blood volume.

Another condition of major clinical importance in which plasma is indicated is a severe burn.

Plasma is also of value in the emergency treatment of acute hemorrhage, since no time is lost because of the necessity of grouping and cross matching. The underlying physiological principles in connection with shock and severe burns apply also to acute hemorrhage, but there are, in addition, certain other physiological changes involved.

After the acute emergency has been met, whole blood must be transfused if the red cell depletion has exceeded the critical amount of from 60 to 75 percent, as no amount of plasma alone will then suffice. The hemoglobin level may be used as a convenient indication for the transfusion of whole blood, it having been suggested that whole blood should be given if the hemoglobin has fallen below 30 percent of normal.

In various *hypoproteinemic states,* the plasma protein level may be below the edema level of approximately 4 percent. Fluid is then lost from the capillaries because of the decreased osmotic pressure of the blood and tissue edema results. Plasma, particularly if administered rapidly, raises the plasma proteins above the edema level, and a dramatic clearing of the edema is frequently observed.

One of the most important questions in connection with the administration of plasma is the amount to be administered in a given case. The important thing is to give the plasma as promptly as possible and in sufficiently large amounts to reverse the abnormal physiological changes which have occurred.

Lee and associates, who have developed a precise mathematical formula for the calculation of the amount of plasma required in a given case, offer the following precept: "Enough plasma should be given to keep the hematocrit value between 50 and 55 percent, and the plasma protein level about 6 gm. per 100 cc. until the capillaries return to a normal state of permeability. At that time enough plasma is given to restore the plasma volume to normal."

In those instances in which it is essential to increase the plasma protein level rapidly without respect to the question of dehydration, *concentrated plasma may be used;* with the desiccated form it is possible to restore the plasma to one-third or one-fourth of its normal volume, and sufficient amounts to obtain a therapeutic result are administered.

X. WOUND HEALING

A. NORMAL WOUND HEALING

Healing by primary intention, the simplest type of wound healing, is best illustrated by the healing of a *simple incision.* Immediately after injury, escaping blood, serum, and lymph coagulate to form the *coagulum,* a dense fibrin network which is filled mainly with erythrocytes and leukocytes. The coagulum may be considered to be a scaffolding which *temporarily unites the edges of the wound.* A type of inflammation, commonly referred to as traumatic inflammation, rapidly develops after injury. There is hyperemia, exudation, and leukocyte immigration in the surrounding tissues, phagocytosis, and enzymatic digestion of devitalized tissue. The increased number of cells observed in the area of traumatic inflammation probably serves as a defense against infection as well as for the removal of dead tissue. Digestion of necrotic material occurs partially by autolysis, by enzymes formed from the injured cells themselves in the form of pepsinase, peptase, arginase, and the like. Heterolysis occurs mainly by reason of the leukocytic enzyme, leukotryptase, which under alkaline conditions digests dead tissue but cannot attack living cells or unchanged connective tissue fibers. As early as the *third day* of wound healing, new vascular sprouts are present. The processes described dominate the picture of wound healing for from *3 to 5 days after injury.* This phase of wound healing, the so-called *lag phase,* may be referred to as the preparatory period to the phase of active tissue regeneration, the phase of fibroplasia which follows.

During the *phase of fibroplasia, which begins 3 to 5 days after injury,* the fibroblasts grow through and along the fibrin network of the coagulum. They originate, divide, and achieve maturity in direct continuity with the edges of the wound. *Simultaneously there is vascularization of the coagulum.* The connective tissue fibrils appear at first as separate delicate fibrils which rapidly increase in number and become firm. Harvey has shown that the velocity of fibroblastic growth begins directly at a maximum and progressively diminishes in rate and that the tensile strength of the wound is the function of the multiplication and maturation of the fibroblasts within the wound. He believes that the other cells involved are relatively unimportant as far as tensile strength is concerned. There is little or no increase in tensile strength during the lag phase. *The phase of fibroplasia is usually complete 10 to 14 days after injury.*

The final phase of wound healing is the *phase of contraction, which may continue for an indefinite period, often for as long as a year.* During this phase the scar tissue becomes more compact and less cellular. The vascular branches are squeezed until many of them are obliterated. *Occasionally the phase of fibroplasia is not terminated in the usual period of*

time, and the proliferating fibroblasts continue to reproduce until a keloid is formed.

B. FACTORS IN WOUND HEALING

1. Systemic

a. Protein Intake. In any attempt to evaluate the condition of a given patient in regard to the probability of healing of wounds, one must consider the patient's state of nutrition, especially in regard to protein intake. Since Thompson, Ravdin, and Frank first demonstrated that wound healing was delayed and that some wounds failed to heal in the presence of hypoproteinemia, studies of patients with wound disruption have confirmed the experimental observation that *serious protein deficiency may be a factor in poor wound healing.* When food can be given by mouth and utilized, 2 to 3 gm. of protein per kilogram daily will supply the daily protein requirements and correct existing protein deficiencies provided the total caloric intake is adequate. The administration of 375 gm. of protein daily for 10 days will elevate a serum protein level 2 gm. per 100 cc. in 10 days, according to the calculations of Elman. When the patient is not able to ingest adequate oral feedings, intravenous injections of blood, plasma, and protein hydrolysates are indicated, but it must be remembered that the intravenous use of any of these substances is not a satisfactory substitute for an adequate diet by mouth.

b. Vitamin Intake. A wealth of data has confirmed the necessity of *vitamin C* for the maturation of precollagen into the collagen of connective tissue fibers and, therefore, the necessity of vitamin C for the healing of all but a few types of tissue. The amount of intercellular substance formed in healing tissues is in direct proportion to the amount of vitamin C available. A vitamin C deficiency with resultant increased capillary fragility may also predispose to hemorrhage from the surfaces of a wound.

Deficiency of *vitamin K* with the resultant *hypoprothrombinemia* may interfere with normal wound healing through *inadequate clotting of blood* and the consequent formation of hematomas and serum collections, which, in turn, predispose to infection and wound separation. Hypoprothrombinemia is prevented by *1 to 3 mg.* of one of the various synthetic vitamin K preparations *together with bile salts* orally daily for 2 to 3 days. If the patient is unable to take oral medication, a water-soluble preparation for parenteral use should be administered.

It is known that deficiencies of the vitamins A, D, C, thiamine, riboflavin, and pantothenic acid lower the rate of phagocytosis and bacterial digestion. Thus, deficiencies of these vitamins might predispose to local wound infection by reducing the efficiency of the defense mechanism of the body against bacterial invasion.

c. Electrolyte and Water Balance. Alterations of the normal electrolyte balance and normal water balance alter the rate of wound healing. *Dehydration* leads to a prolongation of the lag phase and a delay of wound healing. Experience has shown that wounds tend to heal poorly in the presence of *edema.* It has been demonstrated that *acidosis* increases the rate of healing and that *alkalosis* prolongs the rate of wound healing.

d. Anemia. Besser and Ehrenhaft have shown that anemia alone has no effect upon the tensile strength or the histological structure of healing wounds of the stomach of the dog. It is possible that the delayed wound healing observed in many anemic patients may be due to faulty electrolyte balance, faulty fluid balance, nutritional disorders, or combinations of these factors with the observed anemia.

e. Local Temperature. Variations in local temperature have a decided effect upon tissue regeneration. *An increase in the rate of tissue repair has been noted clinically following sympathectomy* and the application of thermal heat in the presence of certain vascular conditions. The favorable results are presumably due to the hyperemia and the increased temperature of the affected parts. *The rate of tissue repair increases with increases in temperature in experimental animals.* Likewise, it would appear that a decrease in temperature as by refrigeration would retard wound healing. Large and Heinbecker, using refrigeration of the extremities of the dog, found a definite lag in the healing of wounds, the degree of delay varying with the duration of the cooling period. They also report a greater number of infections in the cooled extremities as compared with wounds in uncooled extremities.

f. Miscellaneous Factors. The rate of wound healing decreases as the *age* of the patient increases. It is also known that the velocity of wound healing varies with the *size of the wound.* The larger the wound, the greater the initial velocity of wound healing. As the wound heals and becomes smaller, the velocity decreases.

2. Local Factors Which Tend To Delay Healing

a. Trauma.

b. Blood Supply. Restriction of the blood supply to any wound, due either to trauma or unwise ligation of the blood vessels, affects wounds as much as does trauma alone.

c. Hematomas. Hematomas interfere with proper wound healing by preventing apposition of the edges, by prolonging the phase of destruction, and by acting as culture media. Furthermore, the clot interferes with the local circulation through pressure upon the vessels.

d. Chemicals. The use of chemicals for antisepsis should be limited. Most chemicals capable of destroying bacteria also destroy tissue.

e. Electrosurgery. It has been shown that after electrosurgery, or electrocoagulation for hemostasis, the destructive phase is prolonged and wound healing is delayed.

f. Suturing. Suturing under tension or with undue tension causes necrosis along the suture line.

g. Foreign Bodies.

h. Inadequate Apposition. In case of inadequate apposition, dead space must be filled in by granulation.

i. Dehydration. Exposure of wounds to the warm dry air of the operating room and the heat of the operating lights causes dehydration and death of the superficial layers of the exposed areas, and thus adds unnecessary necrotic tissue to the wound and prolongs the destructive phase.

j. Infection.

k. Immobilization and Rest. Mason has stated that motion during the lag period of wound healing disrupts the fibrin bridge and prolongs the lag period. During the proliferative phase, motion may stretch the newly forming scar, with resultant weakening of the delicate new tissues.

C. STATUS OF WOUND-HEALING STIMULANTS

Although numerous reports appear in the literature of the accelerating effect of a great number of topical agents, *the fact remains that there is no generally accepted and proved agent or treatment for accelerating wound healing beyond the normal rate of healing.* The emphasis should be placed on restoring and maintaining a normal physiological state of the body in general, preventing invasive infection by the use of systemically administered antibiotics or sulfonamides and adequate drainage of purulent collections already present.

XI. BURNS

A. CLASSIFICATION OF DEPTH BURNS

Dupuytren (degree)	American (degree)	Name of burn	Converse and Robb-Smith	
			Description	Prognosis
1st	1st	Epidermal	Erythema followed by desquamation.	Heal well.
2d	2d	Dermal	Blistering and superficial destruction of the derma.	Do.
3d	2d	Deep dermal	Destruction to deep layers of derma.	Heal slowly.
Mixed 3d and 4th.	Mixed 2d and 3d.	Mixed burns	Small areas of deep dermal alternate with small areas of deep burns.	Do.
4th, 5th, and 6th.	3d	Deep	Destruction of whole thickness of the skin into or beyond the fat.	Heal with difficulty. Produce contractions unless grafted.

B. PATHOLOGY

1. Local. Burns either injure or kill cells. The cell membranes become abnormally permeable to various substances.

The response to the mildest burn or the response to a severer burn at the point in depth where the burn is minimal is dilatation of the capillaries and the finer arterioles and venules, with markedly increased blood flow through all three after a brief period of vasoconstriction.

After a burn, repair processes start at once. When the damage is minimal, the repair consists of the return of normal tone to the blood vessels, the cessation of leakage, and the absorption of any fluid that is present in the tissue spaces. If cells have been killed, they are removed by lysis and phagocytosis. In case the burn is deep, this process takes place only at the border between the living and the dead cells and the dead cells are sloughed off in masses or sheets. The intercellular collagen resists digestion more than the cells, and the collagen fibers keep the slough attached until they are finally digested at the point of demarcation between the living and the dead parts of the fibers. The repair process may be delayed as a result of local treatment, of infection, or of various deficiencies such as those of iron, protein, or vitamins; but healing cannot be stimulated except by the creation of optimal conditions, so that there is no interference with cell division and cell maturation.

2. Pathology of Red Blood Cells. When sufficient heat penetrates to a depth in the tissue where there are capillaries, some red blood cells are injured.

The occurrence of hemoglobinemia and hemoglobinuria after severe burns has long been known as an indication of a very serious burn. In general, the former is seen only in deep burns of 10 percent or more of the body area and the latter, in such burns of 30 percent area or more.

3. Blood Platelets. In very severe burns, *thrombopenia* of severe degree occurs.

4. White Blood Cells. *Leukocytosis* appearing immediately after the injury and continuing for variable lengths of time has long been known as a constant finding in nearly every burn of moderate or severe extent. The early elevation of the leukocyte count is usually directly proportional to the severity of the burn.

5. Renal Function. Impairment of renal function, as evidenced by anuria, oliguria, and azotemia, is a conspicuous feature in the early course of patients with severe burns. Albumin, hemoglobin, and casts are frequently found in the urine of these patients, whereas large numbers of white or red blood cells are rare. The blood flow through the kidney may be decreased to one-twentieth of the normal at a time when the general blood flow is reduced only to one-half. This is true particularly in burn shock, in which the vasoconstriction at any given peripheral blood pressure seems to be significantly greater than in other types of shock.

It has also been suggested that the kidney failure of burns is caused by the hemoglobin that is excreted in some cases. This is suggested by the histological changes in the kidney, which are similar to the changes in patients with hemoglobinuria due to causes other than burns.

The first urine of patients with severe burns is almost invariably strongly acid, and immediate administration of alkali to the patient has been recommended. The purpose of this alkalization is to prevent precipitation of the products of the destroyed red cells in the renal tubules in the presence of an acid urine.

6. Pathology of the Liver. In 1941, Wells, Humphrey, and Coll, by clinical and experimental work, definitely showed that necrosis was due to tannic acid poisoning.

7. Pathology of the Kidney. The most consistent anatomical changes are the following: On *microscopic* examination, the glomeruli are normal and the tubules show varying degrees of necrosis affecting principally the ascending and descending portions of the loops of Henle. Pigmented casts in the tubules are a constant finding in these cases.

The findings of *gross examinations* are essentially normal. In a few cases the kidneys were *swollen,* the *cortices pale,* and the *medullae dark red,* presenting prominent black, brown, or purple-red streaks converging toward the papillae. Goodpastor and associates believe that the important etiologic factors of injury to the kidney in burns are the presence of marked hemoglobinemia, hemoglobinuria, and severe shock.

8. Pathology of the Gastrointestinal Tract. The occurrence of ulceration of the intestinal tract following burns has been recognized for over 100 years.

The cause of the ulcers has not been determined.

9. Respiratory Tract. The respiratory damage is essentially that of a *laryngotracheobronchitis.*

C. METABOLIC CHANGES IN BURNS

1. Electrolyte Metabolism. The findings of a decrease in plasma chloride concentration in the first few days following an extensive burn, first reported by Davidson in 1926, has since been confirmed by a number of workers. These later studies have also demonstrated a decrease in serum sodium concentration and a decrease in urinary sodium and chloride excretions.

A shift of some sodium into the injured cells in the burned area with a shift from the injured cells of an equivalent amount of potassium has been demonstrated. The actual rise in circulating plasma potassium concentration is small and well below the toxic range for normal animals.

2. Nitrogen Metabolism. All severely burned patients who are neither anuric nor too severely oliguric have a high output of nitrogen in the urine during the first 3 weeks, and, in a few cases, this output continues for many months. Steady losses of from 25 to 30 gm. of nitrogen per day have been observed frequently, and on an occasional day the loss may be as high as 45 gm. The cause of the excessive nitrogen excretion has not been finally determined.

While large quantities of nitrogen are being lost in the urine and in the drainage from the wounds of such patients, the protein intake is likely to be greatly reduced by reason of pain, anorexia, and poor gastrointestinal function. The negative nitrogen balance occurring under these conditions may have serious effects in a few days in a patient with already depleted body protein and, in a few weeks, in a patient with excellent protein nutrition. This is reflected in the development of a progressive hypoproteinemia. This is an extremely serious metabolic sign. During the first week following a burn, a transitory hypoproteinemia may be present; it is due to shifts of water, electrolyte, and protein from the blood stream into the subcutaneous tissue or exudate. This early hypoproteinemia is without nutritional significance. On the other hand, a continuous fall in plasma proteins after the first week is a sign of marked tissue protein deprivation.

3. Carbohydrate Metabolism. Hyperglycemia, lactacidemia, and lowered carbon dioxide combining power are frequently found in human beings and animals following burns. The extent and duration of the changes in these blood constituents are roughly proportional to the severity of the burn.

The adrenal glands may play an important role in the production of abnormalities in carbohydrate metabolism following burns, although the entire picture cannot be explained on this basis.

4. Vitamins. Increased demands for vitamins in burns have been suspected for some time by analogy with studies showing increased needs for vitamins in other diseases.

The extra needs for vitamins commence with the burn and remain until healing is complete. In general, the extra amounts needed to prevent depletion parallel the area of unhealed burn. The maintenance of such levels will, in very severe cases, entail the administration of up to 2.0 gm. of ascorbic acid, 50 mg. of thiamine, 50 mg. of riboflavin, and 500 mg. of nicotinamide (niacinamide).

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9. Respiratory Tract. The respiratory damage is essentially that of a *laryngotracheobronchitis.*

Symbiotic infections, in which an anaerobic or microaerophilic streptococcus is associated with one or more other organisms, occur rarely. Under the conditions there may be burrowing of the infection at the edge of the wound and destruction of otherwise viable tissue.

F. HYPERPYREXIA IN BURNS

Patients with burns frequently have a period of high fever in the first few days after the burn. The pathogenesis of this early high fever is not known.

The burn patient cannot tolerate a high fever; hence if the rectal temperature remains above 41° C. for more than a very few hours, death is almost certain. Prompt and energetic treatment directed toward cooling the patient is effective in many instances, and this treatment should be started whenever the rectal temperature is above 40° C.

G. TREATMENT

1. Primary Local Treatment. There is still no general agreement as to primary local treatment. Recently, however, certain fundamental conceptions have been widely accepted and have led to a more nearly unified view of treatment. *The first of these is that the care of local areas in a patient with burns of any important size is but part of the total treatment of the patient. The second is that the treatment of the patient should be based on methods to correct as far as possible the many physiological and pathological changes brought about by the burn. Local plasma loss should be limited, further contamination prevented, and infection controlled. Any surface application should cause no local or general toxic effects. Application of the treatment should be rapid and relatively easy, and the least possible attention should be required thereafter.*

a. Fluid loss. In addition to the harm done by the loss of fluid from the circulation by causing shock, the fluid is harmful to the subcutaneous tissues because it clots there and increases the extracellular pressure with resulting increased fibrous tissue. From the point of view of both local and systemic reactions, one of the features to be desired of any local treatment is that it limit the amount of internal and external fluid loss.

b. Local Tissue Injury Caused by Surface Treatment. It has been shown that the escharotics, as opposed to bland ointments, injure viable epithelium. Healing of dermal burns of the back takes place a few days earlier if ointment is used rather than either tannic acid and silver nitrate or triple dye. Epithelization under a dry gauze pressure or saline pressure dressing proceeds at the same rate as under a petrolatum dressing.

c. Systemic Effects of Substances Applied Locally to the Burned Area. Absorption of certain types of substances from the surface of both second- and third-degree burns has been demonstrated. It is important that any agent used in the treatment of the burned area either be not absorbed, or, if absorbed, be relatively nontoxic. Jaundice and other evidences of liver damage are seen more frequently in patients treated with tannic acid than in those treated with bland ointments.

Boric acid has no particular virtues, and, since it may be absorbed in toxic amounts if applied over a large area of injured skin, it had best be avoided and simple petrolatum used.

D. BURN SHOCK

Burn shock may be defined as a condition of low blood plasma volume, low cardiac output, low blood pressure, and increased peripheral resistance to blood flow. The four factors that have been considered important as causes of burn shock are: (1) Loss of circulating plasma, (2) toxic substances in the blood, (3) pain, and (4) cold.

1. Diagnosis. Careful estimation of the area and of the approximate depth of a burn is important for the anticipation of shock. Any patient with a burn area of 15 percent or greater will probably suffer from shock, and any patient with a burn area of 25 percent will probably suffer from fatal shock, unless prompt and active treatment is given.

Hematocrit, hemoglobin, and red blood cell determinations are useful. Except for research purposes, serial determinations at 2- to 3-hour intervals of any one of these is sufficient. The blood examination must be made venous rather than capillary blood because of stagnation in the capillaries.

Serial plasma protein determinations also provide useful information. As *plasma is lost from the vascular bed, there is a shift of low protein,* extravascular (chiefly interstitial) fluid into the blood stream. This results in dilution of the plasma protein.

Accurate records of urine output must be kept. If the urine output is good, one may feel sure that the general circulation is good; if, however, the output falls, one must anticipate early failure of the general circulation.

2. Secondary Effects. The effects of severe burns without shock and of severe shock without burns are similar in many instances. For instance, increases in the blood sugar, lactic acid, nonprotein nitrogen, amino acids, ammonia, and hydrogen ion concentration and decreases in sodium chloride and ascorbic acid are common to both.

Another complication of burn (and other forms of) shock is "irreversible" shock. *If the systolic blood pressure remains below 50 mm. for more than* 3 or 4 hours, the shock is almost surely "irreversible," and frequently it may become so in a shorter time.

3. Prevention and Treatment. The first principle of treatment of any form of shock is to avoid any procedure that will increase the shock and to postpone necessary shocking procedures (such as dressings) until shock has been prevented or treated. Of these measures, those that restore and maintain the blood volume are of paramount importance.

E. INFECTION IN BURNS

1. Initial Contamination. A burn immediately after the accident harbors few pathogenic organisms, since the process of burning sterilizes the skin in the affected area. However, unless protected, the lesion is rapidly contaminated.

2. Bacteriology. The *hemolytic streptococcus* is usually the predominant infecting organism. Burns at all stages are almost always contaminated or infected with several organisms. Aerobic, anerobic, gram-positive and gram-negative bacteria, and cocci may all be found in any single culture. The hemolytic staphylococcus is often the predominant pathogenic organism.

Symbiotic infections, in which an anaerobic or microaerophilic streptococcus is associated with one or more other organisms, occur rarely. Under the conditions there may be burrowing of the infection at the edge of the wound and destruction of otherwise viable tissue.

F. HYPERPYREXIA IN BURNS

Patients with burns frequently have a period of high fever in the first few days after the burn. The pathogenesis of this early high fever is not known.

The burn patient cannot tolerate a high fever; hence if the rectal temperature remains above 41° C. for more than a very few hours, death is almost certain. Prompt and energetic treatment directed toward cooling the patient is effective in many instances, and this treatment should be started whenever the rectal temperature is above 40° C.

G. TREATMENT

1. Primary Local Treatment. There is still no general agreement as to primary local treatment. Recently, however, certain fundamental conceptions have been widely accepted and have led to a more nearly unified view of treatment. *The first of these is that the care of local areas in a patient with burns of any important size is but part of the total treatment of the patient. The second is that the treatment of the patient should be based on methods to correct as far as possible the many physiological and pathological changes brought about by the burn. Local plasma loss should be limited, further contamination prevented, and infection controlled. Any surface application should cause no local or general toxic effects. Application of the treatment should be rapid and relatively easy, and the least possible attention should be required thereafter.*

a. Fluid loss. In addition to the harm done by the loss of fluid from the circulation by causing shock, the fluid is harmful to the subcutaneous tissues because it clots there and increases the extracellular pressure with resulting increased fibrous tissue. From the point of view of both local and systemic reactions, one of the features to be desired of any local treatment is that it limit the amount of internal and external fluid loss.

b. Local Tissue Injury Caused by Surface Treatment. It has been shown that the escharotics, as opposed to bland ointments, injure viable epithelium. Healing of dermal burns of the back takes place a few days earlier if ointment is used rather than either tannic acid and silver nitrate or triple dye. Epithelization under a dry gauze pressure or saline pressure dressing proceeds at the same rate as under a petrolatum dressing.

c. Systemic Effects of Substances Applied Locally to the Burned Area. Absorption of certain types of substances from the surface of both second- and third-degree burns has been demonstrated. It is important that any agent used in the treatment of the burned area either be not absorbed, or, if absorbed, be relatively nontoxic. Jaundice and other evidences of liver damage are seen more frequently in patients treated with tannic acid than in those treated with bland ointments.

Boric acid has no particular virtues, and, since it may be absorbed in toxic amounts if applied over a large area of injured skin, it had best be avoided and simple petrolatum used.

D. BURN SHOCK

Burn shock may be defined as a condition of low blood plasma volume, low cardiac output, low blood pressure, and increased peripheral resistance to blood flow. The four factors that have been considered important as causes of burn shock are: (1) Loss of circulating plasma, (2) toxic substances in the blood, (3) pain, and (4) cold.

1. Diagnosis. Careful estimation of the area and of the approximate depth of a burn is important for the anticipation of shock. Any patient with a burn area of 15 percent or greater will probably suffer from shock, and any patient with a burn area of 25 percent will probably suffer from fatal shock, unless prompt and active treatment is given.

Hematocrit, hemoglobin, and red blood cell determinations are useful. Except for research purposes, serial determinations at 2- to 3-hour intervals of any one of these is sufficient. The blood examination must be made venous rather than capillary blood because of stagnation in the capillaries.

Serial plasma protein determinations also provide useful information. As plasma is lost from the vascular bed, there is a shift of low protein, extravascular (chiefly interstitial) fluid into the blood stream. This results in dilution of the plasma protein.

Accurate records of urine output must be kept. If the urine output is good, one may feel sure that the general circulation is good; if, however, the output falls, one must anticipate early failure of the general circulation.

2. Secondary Effects. *The effects of severe burns without shock and* of severe shock without burns are similar in many instances. For instance, increases in the blood sugar, lactic acid, nonprotein nitrogen, amino acids, ammonia, and hydrogen ion concentration and decreases in sodium chloride and ascorbic acid are common to both.

Another complication of burn (and other forms of) shock is "irreversible" shock. If the systolic blood pressure remains below 50 mm. for more than 3 or 4 hours, the shock is almost surely "irreversible," and frequently it may become so in a shorter time.

3. Prevention and Treatment. The first principle of treatment of any form of shock is to avoid any procedure that will increase the shock and to postpone necessary shocking procedures (such as dressings) until shock has been prevented or treated. Of these measures, those that restore and maintain the blood volume are of paramount importance.

E. INFECTION IN BURNS

1. Initial Contamination. A burn immediately after the accident harbors few pathogenic organisms, since the process of burning sterilizes the skin in the affected area. However, unless protected, the lesion is rapidly contaminated.

2. Bacteriology. The *hemolytic streptococcus* is usually the predominant infecting organism. Burns at all stages are almost always contaminated or infected with several organisms. Aerobic, anerobic, gram-positive and gram-negative bacteria, and cocci may all be found in any single culture. The hemolytic staphylococcus is often the predominant pathogenic organism.

4. Chronic Anemia. The anemia is *progressive,* and its *chronicity and severity are roughly proportional to the extent of unhealed deep burn.* It does not respond to large intakes of iron, liver extract, protein calories, and vitamins, although these must be given for nutritional purposes. *Blood transfusions are necessary at frequent intervals and in large amounts to maintain the hemoglobin at a satisfactory level.*

5. Sex Hormones. In severely burned young women, menses cease and do not commence again until healing is nearly complete. These patients develop an abnormal growth of hair, especially on their arms and legs. This hair disappears at about the same time that menses recommence. Testosterone propionate has been used with considerable clinical success in the late stages of burns. The dose used is 10 mg. per day, given intramuscularly. This hormone has produced good effects in patients of both sexes.

d. Prevention of Infection. Strict aseptic technic in the handling of burned patients is necessary to prevent additional contamination of the wound.

(*1*) *Washing and Debridement of Burns.* Routine washing of burns has recently been shown not to be necessary if pressure dressings or casts are used. *However, it is generally agreed by those who do wash burns that it* should be done gently and quickly. White soap has been most commonly used rather than tincture of green soap.

(*2*) *Prevention of Further Contamination.* Pressure dressings or casts which remain dry on the outside prevent the entrance of additional organisms. If, however, the dressing becomes saturated with exudate, contamination is possible.

Dressing should be done at infrequent intervals. The first dressing should remain in place for about 2 weeks. At the end of this time most dermal burns are healed and require no further dressing, but deep dermal, mixed, and deep burns are just beginning to slough.

(*3*) *Immobilization.* The absorption of toxic products, metabolic or bacterial, depends to a large extent on the lymphatic flow, which is reduced considerably by rest of the injured part.

(*4*) *Chemotherapeutic Agents.* These agents have been widely used for the control of infection of burns. The sulfonamides have been used both locally and systemically, but their efficacy in controlling the local infection of the burn has not been clearly demonstrated.

Penicillin has been used locally and systematically in many cases of serious burns. When used locally it has the great defect of rapid absorption from the wound. When given intramuscularly, penicillin has not been shown to reduce in any way the hemolytic staphylococcus infection of a burn.

2. Secondary Surface Treatment. The first pressure dressing or cast should be left in place for 2 or 3 weeks except in the few very superficial dermal burns that have probably healed prior to this time. A foul odor, contamination of the dressing by urine or feces, and evidence of infection under the dressing should rarely be considered indications for a change at any earlier time.

As soon as large areas have become free of slough and if the granulations and the patient are both in good condition, grafts should be applied without waiting for the adjacent slough to separate.

Skin Grafting After Sloughing. In most clinics, burns are grafted in the granulating stage. The time that the slough is completely separated is usually between the third and sixth weeks. Sloughs on small and more vascular areas, such as the face, separate more quickly than those on larger and less vascular areas.

3. Nutrition. *Failure to meet the increased nutritional demands of the severely burned patient results in progressive loss of weight and strength, edema, friable granulations, increased local infections, and, finally, death from malnutrition. The principal foodstuff required is protein.* However, the food provided must be an adequate metabolic mixture containing, in addition to adequate amounts of protein, sufficient calories, carbohydrates, minerals, water, and accessory food substances.

vide the amino acids essential for a good nutritive state. Frequently the deficiency results from an intake quantitatively and qualitatively inadequate.

2. Impaired Digestion and Absorption of Protein. These conditions are found in certain chronic diseases of the gastrointestinal tract associated with abnormalities in the secretory activity of the stomach, small intestine, pancreas, or liver.

3. Impaired Protein Synthesis. The liver is inseparably associated with protein synthesis. It is generally agreed that albumin and fibrinogen are formed in it, and certain globulin fractions are without doubt normally synthesized in part in the liver. Addis and his associates demonstrated that the liver contains under normal conditions a readily mobilizable reserve store of protein which is depleted during fasting and restored after adequate feeding. Addis has called this readily depleted protein "labile protein."

The protein deficiency which results from serious hepatic disease may not be due to an insufficient protein intake, although the latter may be a factor in the milder cirrhoses. It is due to a fundamental disturbance of function which prevents the liver from utilizing in a normal manner the amino acids as building stones for protein synthesis.

4. Increased Loss of Protein From the Body. Some protein, in the form of the nitrogenous products of protein catabolism, is constantly excreted in the urine. This is a normal mechanism and provides for the disposal of such nitrogenous material as is no longer useful in the body economy.

The amount of protein lost in the urine in certain lesions of the kidney may, however, be so great that under none of the conditions now available can the protein deficiency be corrected until a more nearly normal renal function is established. The fraction of the serum protein which suffers to the greatest degree is the albumin.

The significance of an anemia, especially a marked reduction of the hemoglobin in the presence of a protein deficiency, should be clearly understood.

Whipple has summarized this relationship as follows: "We believed that in a dog, both anemic and plasma depleted, we could influence the protein flow toward hemoglobin by one food factor or toward plasma protein by another food. . . . To our surprise we observed that such dogs (hemoglobin and plasma protein deficient (always produce more hemoglobin than plasma protein no matter what diet protein is used. . . . Hemoglobin in its production may draw on the plasma protein but hemoglobin stands apart in the protein economy and does not contribute freely to the protein pool. On the other hand, the body guards jealously the fabrication of hemoglobin and given a real need for both plasma protein and hemoglobin the protein flow favors hemoglobin, which under these circumstances is produced in more abundance than the plasma protein." Every possible effort, therefore, should be made to correct an existing anemia in protein deficient surgical patients.

5. Increased Catabolism of Protein in the Body. Some protein is constantly being broken down in the normal processes of metabolism. In fever, in hyperthyroidism, as well as in other conditions associated with an increase in the metabolic rate, such as myelogenous leukemia, there occurs a marked increase in the rate of protein break-down. In the severe infec-

XII. PROTEIN IN SURGERY

Normal growth and normal utilization of protein depend upon the presence of eight to ten essential amino acids.

Proteins are an important part of all cells, including the nuclei. The enzymes, hormones, and antibodies of man are in the main protein in character. The plasma proteins, through their colloid osmotic effect, play an important role in maintaining normal relations between intracellular and extracellular body fluid.

The plasma proteins consist of two main groups, the albumins and the globulins. Each of the subfractions has specific physiological functions. Serum albumin is responsible for approximately 85 percent of the colloid osmotic effect of the plasma proteins. Fibrinogen, prothrombin, and the antibodies are found in the globulin fractions. Protein undernutrition is first manifested by a fall in serum albumin concentration, although, if means to determine it were available, the first effect of protein undernutrition is a reduction in the amount of protein stored in the tissues of the body, since every attempt is made to maintain the serum protein concentration at a nearly normal level. *In this sense hypoproteinemia, either in the total of circulating protein or in its concentration, is indicative of a reduction in the "labile," or reserve, stores of body protein.*

The determination of *nitrogen balance* is important in protein nutrition, for only by this means can it be known whether protein is being stored in the body or lost from it. A person is in *positive nitrogen balance if the intake of nitrogen by mouth or parenterally exceeds the amount lost from the body by all means and in negative nitrogen balance if the output exceeds the intake.* In considering output, it is important to take into account not only the output in the urine but also that lost from wounds and through suppuration. *A negative balance occurs when there is excessive break-down of body protein, abnormal loss from any source, or inadequate protein intake. A positive balance occurs when the intake of foodstuffs is adequate both in the amount of protein and in the total calories.* Although a positive nitrogen balance may be obtained on a relatively low protein intake if the caloric intake, especially of carbohydrate, is adequate, such a dietary is not safe over long periods, for it does not provide for sudden demands during illness or injury.

A. CAUSES OF PROTEIN DEFICIENCY

In general there are five major causes of protein deficiency.

1. Insufficient Intake of Protein (Chronic Malnutrition). Chronic malnutrition results when there is an inadequate intake of protein to meet the nutritive and metabolic demands of the body. There may be an absolute quantitative deficiency in protein intake, or the protein, while quantitatively sufficient, may be qualitatively inadequate in that as ingested it fails to pro-

follows their use may increase the circulating volume to a degree which may lead to cardiac embarrassment. These substances are very useful during temporary periods of hepatic insufficiency, but they are expensive and evidence is available that they do not serve adequately for long periods as the only source of protein in the presence of serious protein deficits.

Casein, lactalbumin, and fibrin hydrolysates have been widely used intravenously, reinforced with glucose to increase the total caloric intake. It has been found that when they are administered in sufficient amounts—0.5 gm. of nitrogen and 30 calories per kilogram of body weight per day—a positive nitrogen balance can usually be maintained.

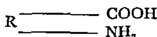
Gelatin has proved to be an excellent plasma substitute when an acute plasma deficiency exists. Gelatin is, however, not a complete protein, in that it is lacking in certain of the essential amino acids; hence it is an unsatisfactory source of nutritional protein. Recently Brunschwig has published data which suggest that with gelatin, reinforced with the necessary essential amino acids which are lacking in it, a positive nitrogen balance can be maintained.

Whole blood is useful in overcoming an anemia in protein-deficient patients, but it is not an economical source of protein in protein deficiency.

a. Amino Acids. Amino acids may be given parenterally in one of two ways: (1) *As such*, or (2) *in the form of a solution of hydrolyzed protein* so prepared as to yield a more or less complete mixture of amino acids and, in certain hydrolysates, small peptides.

An obvious defect in most acid hydrolysates is the fact that the essential amino acid tryptophan is destroyed during digestion. The necessity of adding tryptophan makes the cost unduly high. Fortunately, an enzymatic hydrolysate of casein is now available that requires no supplementation.

Relation of Amino Acids to Protein. There are 21 or more amino acids, each different, although all conforming to the same general chemical formula in that they contain an amino and a carboxyl group.



Most important is the fact that only 10 or 11 of them may be considered as "essential." These essential amino acids are also termed *indispensable* because the body is unable to manufacture them from simpler material and they must, therefore, be supplied before normal protein metabolism can occur.

List of the Various Amino Acids in Protein

Indispensable	*Dispensable*
Lysine	Glycine
Tryptophan	Alanine
Histidine	Serine
Phenylalanine	Norleucine
Leucine	Aspartic acid
Isoleucine	Glutamic acid
Threonine	Hydroxyglutamic acid
Methionine	Proline
Valine	Hydroxyproline
Arginine	Citrulline
	Tyrosine

tions, even those unassociated with suppuration, a rapidly developing hypoproteinemia may be observed.

Cannon and his associates, in a series of important contributions, have pointed out the *close relationship existing between protein deficiency and an inability to develop adequate antibodies.*

The body requirements of protein cannot fail to be met, even for relatively short periods, in persons subjected to serious acute illness or injury, without profound physiological changes. *When a deficiency of such requirements occurs over relatively protracted periods, morbidity is increased, convalescence is retarded, and the mortality of a variety of conditions is increased.* When it is considered that after even relatively minor operations there takes place a marked increase in protein catabolism and after major procedures a more extensive protein break-down, the significance of an adequate nutritive state becomes even more apparent.

B. PROBLEMS OF PROTEIN DEFICIENCY

Lund and Levenson, in an excellent review, have called attention to the importance of *correcting protein deficiencies in shock, in local or general hypoproteinemic edema, in the healing of wounds, in infection, and in the detoxification of certain noxious substances.* To these should be added the importance of correcting a protein deficiency during convalescence, for it is at such a period that a great deal can be accomplished in facilitating a speedy and complete recovery.

Every operation, every injury, and every infection is associated with a period of increased nitrogen catabolism resulting in most instances in a negative nitrogen balance.

1. Correction of Protein Deficiency. The best route to supply the energy requirements of a patient and to add to the various stores of body foodstuffs is the *oral route.* When there exists no contraindication to oral or orojejunal feeding, other routes should not be used except for *supplementary feeding.*

The ordinary patient does well on a protein intake of *1 gm. per kilogram of body weight per day.* In extensive superficial burns and extensive trauma of other types, and in severe infections, especially those associated with suppuration, the protein intake should be greatly increased. A positive nitrogen balance may not be obtainable in the presence of acute injury or infection under any program of feeding. Not only are large amounts of protein often necessary—amounts as high as 300 gm. per day—but the total caloric intake should likewise be increased from 2,000 to 2,500 to 3,500 to 4,000 calories a day.

After the immediate crisis of the operation has passed, the patient should be placed on a diet containing 125 to 150 gm. of protein with sufficient carbohydrate and fat to provide from 2,600 to 3,000 calories per day. It is possible to use protein hydrolysates by tube into the stomach or jejunum in conjunction with glucose and even fat.

Protein can be administered as human plasma or human albumin, as hydrolysates of casein or fibrin, as gelatin, or as whôle blood.

Large amounts of plasma or albumin intravenously may be used for replenishing chronic protein deficits. The increased blood volume which

The second method depends upon the use of proteolytic enzymes of one type or another. Both methods for preparing amino acid mixtures in the form of protein hydrolysates have certain possible shortcomings. The methods may involve the loss of some of the essential amino acids during the hydrolysis, but this liability may be avoided by the use of appropriate procedures; moreover, the resultant digest can be tested both chemically and biologically for the presence of all of the essential amino acids, and missing ones added. Another possible disadvantage of using protein hydrolysates as a source of amino acids is the addition of deleterious substances during manufacture; apparently this can also be avoided by carefully conducted procedures. A final possible objection is the presence of peptides as well as amino acids in the final mixture; this occurs with enzymic hydrolysis, but actually it may not be an objection at all. As long as digestion has been sufficient to remove all traces of protein molecules and the resultant product is shown to have no anaphylactogenic substances, no danger seems to arise from the mere presence of peptides.

For parenteral use, amino acid mixtures, either as such or in the form of hydrolysates, should probably fulfill the following specifications:

(*a*) They must be fairly soluble in water and, at a moderate rate of intravenous injection, provoke no significant incidence of pyrogenic or other untoward reactions.

(*b*) They must be able to support positive nitrogen balance when given intravenously as the sole source of nitrogen.

(*c*) They must be able to provoke a regeneration of serum protein in depleted animals or human beings when injected intravenously as the sole source of nitrogen.

(*d*) They should contain a sufficient proportion of all of the essential amino acids.

Protein hydrolysates at the present time are the only generally available means of using amino acid mixtures for parenteral alimentation. Moreover, only two preparations are on the market. *One of them is an acid hydrolysate of casein containing only amino acids fortified with tryptophan; the other, an enzymic hydrolysate of casein and pork pancreas containing both amino acids and small peptides.*

The following data have been submitted by the manufacturer and are of interest in describing the properties of this hydrolysate. A high grade of acid-precipitated casein and carefully selected pork pancreas are mixed in water, held at a constant temperature, and protected against contamination. The mixture is then inactivated by heat, the pH adjusted, and the solution decolorized and filtered. It is concentrated under reduced pressure, pasteurized, and finally dehydrated to a fine powder. The final product is tested first by being fed to experimental animals as the sole source of nitrogen, and a normal rate of growth observed. Anaphylactic studies are carried out by employing guinea pigs, which first receive an injection of Amigen and, subsequently, injections of Amigen, skimmed milk, and pork pancreas extract. The absence of anaphylactic reaction is taken as an indication that the product is nonantigenic. Although bacteriological control is maintained throughout the process of manufacture and although the Amigen powder shows a low bacterial count, *sterility is not achieved.* How-

Each protein in the body as well as each protein in food has its own individual amino acid composition. *Transfers from one protein to another requires a break-down of the protein molecule into its individual amino acids and the reassembling of them to form another protein.* This general procedure is the normal method by which food protein is transformed into tissue protein. Hydrolysis or digestion occurs in the gastrointestinal tract; the resulting amino acids are absorbed into the portal system, and *synthesis of these building stones then takes place in the liver or other tissues.* Extra-alimentary transfers, as the use of tissue protein in the synthesis of new serum protein after its loss in a hemorrhage, are assumed to involve a similar mechanism.

2. Preparation of Amino Acids for Intravenous Use. Amino acids are available in crystalline form and may be purchased on the open market. They may then be combined in exact proportions and dissolved in water, sterilized, and given by injection. The large amount of protein nourishment needed in terms of crystalline amino acids makes their employment impracticable until such a time as they are produced cheaply enough to permit general use. The accompanying table, drawn up by Albanese, summarizes the advantages and disadvantages of pure crystalline amino acids as a source of parenteral protein nutrition, as compared with amino acids made by hydrolysis of natural proteins.

Protein Hydrolysates vs. Crystalline Amino Acid Mixtures as Intravenous Protein Nourishment

Criteria	Protein hydrolysates	Crystalline amino acid mixtures
Purity	Virtual freedom from unnatural optical isomers	Freedom from nonamino acid impurities
Utility	Composition readily varied by supplementation, less readily by degradation.	Composition can be readily varied.
Metabolic stress	Synthesis of unessentials is avoided	Deamination and excretion of (unneeded) unessentials is avoided
Toxicity	Toxic effects attributed to unnatural isomers (e. g., phenylalanine) are avoided	Toxic effects attributed to unessentials (e. g., glutamic acid) are avoided.
Speed of administration	More rapid injection of crystalline mixture may not mean more rapid utilization, because of greater loss in urine	More rapid injection is possible
Adequacy	1. Possibility that some "unessential" amino acid may prove essential 2. Possibility that hydrolysates may contain an undiscovered amino acid that is essential.	
Availability	Generally available	Not generally available.

Amino acid mixtures may be made in vitro by hydrolysis or digestion of natural proteins. This procedure is essentially similar to that by which the body produces amino acids from the protein food in the gastrointestinal tract and is both practical and cheap. *Two general methods for the digestion of protein are available. One involves the use of inorganic chemicals, such as acid and alkali, and physical methods, such as heat and increased pressure.*

Fate of amino acids after intravenous injection. The eventual behavior of amino acids after they leave the blood stream is not known in detail, although it would seem that basically it probably differs very little from the metabolism of amino acids absorbed into the portal circulation. *The injected amino acids undergo one or more of three changes: (1) Some are metabolized into nonprotein nitrogenous substances, such as creatine, purine, etc.; (2) others are deaminized, the nitrogen converted to urea and the rest utilized as carbohydrate or to form other amino acids; (3) the remainder are synthesized to form tissue or other protein, hormones, etc.* That relatively little is lost as urea and that protein synthesis actually occurs is shown by the fact that the injection of adequate amino acid mixtures leads to the achievement of positive nitrogen balance and to increases in serum albumin even when no other form of protein nourishment is given.

5. Therapeutic Use of Amino Acids. As a means of supplying *acute protein deficits* following surgical shock and hemorrhage, amino acids have the same disadvantage as simple solutions of glucose and saline in that *they possess no colloidal properties.*

Amino acids as a source of protein food are quite similar to glucose as a source of carbohydrate food. Appropriate mixtures of amino acids as such or as hydrolyzed protein, therefore, represent a physiological method for introducing protein nourishment outside the gastrointestinal tract.

The details of dosage and administration are determined by the purpose for which they are given: *(1) to correct cumulative deficits in chronic depletion; (2) to prevent protein starvation after operation by meeting the daily needs for protein;* and *(3) to supplement the normal oral intake.*

(1) To Correct Cumulative Deficits. The correction of chronic deficits in malnourished patients who for a long time have been unable to eat normally presents a large, quantitative problem, inasmuch as these deficits are cumulative. A patient who has lost 50 pounds of body weight has probably lost at least a fifth of it as protein tissue, or, in terms of dry protein, 2,000 gm. The complete replacement of all this amount of protein through the intravenous injection of amino acids and plasma, while theoretically possible, is so difficult that thus far, at least, no one has apparently tried to do so. In actual practice it may not be necessary to replace these losses completely. The clinical benefit that follows even partial correction is considerable. A moderate amount of parenteral protein nourishment that can be given to these patients would be about twice what might be called the daily need, i. e., about 100 to 150 gm. per day. This represents, in the case of Amigen, 2 to 3 liters of a 5-percent solution (plus 5 percent glucose).

(2) To Prevent Protein Starvation. This can be achieved by meeting the daily requirements of protein nourishment. Under the simplest conditions 1 liter of fluid containing 5 percent Amigen (plus 5 percent glucose) would be considered a minimum requirement. However, after severe operations the loss of nitrogen is great and there is certainly a greater need for protein. At least 2 liters of this solution are therefore indicated, particularly when a deficiency was present before the operative procedure.

(3) To Supplement Oral Intake. Supplementary injections of amino acids may occasionally be employed to augment a deficient oral intake of protein.

ever, hemolytic cocci and B. coli must be absent. Injection tests are made routinely in both anesthetized and unanesthetized dogs to be sure that the product has no abnormal effect on blood pressure, respiration, or temperature, and that it produces no other ill effects. Amigen is received as a fine, impalpable powder almost white in color and with very little odor. It is soluble in water up to about 15 percent with slight warming and produces a crystal-clear amber-colored solution with a pH of 5.5. For intravenous use, a mixture of 5 percent Amigen and 5 percent glucose, neutralized to a pH of 6.5, is usually prepared.

In *preparation of sterile Amigen solutions, immediate* sterilization is essential; a delay of several hours after the solution is made up may permit sufficient growth to lead to pyrogenic reactions even if the solution is still crystal clear and the bacteria are subsequently removed or killed.

Two general methods for the sterilization of Amigen solutions have been employed: Autoclaving, and *adequate filtration.* Sterilization by means of the autoclave is the surest way, but it has the disadvantage that some darkening will occur, which is increased if glucose is also present.

3. Contraindications to Injection of Amino Acids. The most obvious immediate contraindication is the *presence of turbidity or precipitate in the solutions.* Only crystal-clear solutions should be injected.

The administration of any protein food during the course of *acute renal impairment* is said to be contraindicated because it inevitably leads to the need for the excretion of additional ammonia and urea, which imposes an additional excretory task upon the kidney.

Only one specific contraindication to the intravenous injection of amino acids has been expressed and that is the presence of *severe hepatic disease.*

The intravenous injection of amino acids should always be discontinued in the presence of any reaction, even though it is a *simple pyrogenic reaction.* However, this should not be counted as a contraindication to further injections except when the reaction is one of allergic sensitivity.

4. Metabolism of Amino Acids Given Intravenously. In order to evaluate the metabolism of intravenously injected amino acids, the differences between the oral and parenteral administration must be evaluated.

Differences between oral and parenteral administration. The utilization of amino acids injected into the systemic circulation as compared with their absorption into the portal circulation differs in at least three ways. First of all, there is the *influence of the liver.* On a theoretical basis it might be assumed that the introduction into the peripheral vein would be advantageous in that deaminization by the liver would be less extensive and that amino acids would reach tissues more rapidly and directly and thus permit more efficient utilization. The *second* difference between the intravenous and the oral route is the fact that all amino acids injected into the blood necessarily reach the tissues at the same time. This would seem also to increase the likelihood of efficient utilization. A *third* difference is based on the possible influence of bacterial action in the intestines on the amino acids before they are absorbed.

Actual observations, for the most part, have so far shown very little difference in the utilization of amino acids, whether they are injected into peripheral veins or absorbed from the gastrointestinal tract.

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XIII. VITAMINS IN SURGERY

The vitamins are of great importance to the surgical patient because of the prominent role they play in *general nutrition, resistance to infection, cardiac reserve, healing of wounds, and prevention of hemorrhage.*

A. VITAMIN A

Vitamin A is formed from ingested *carotene*, probably in the liver, where large amounts of it may be stored. About 95 percent of all the vitamin A in the body is held in the liver, and the reserves so stored can be built up to supply the body's needs for a long time. The average daily requirement for man is not accurately known. Since it is stored in the liver and also is fat-soluble, large amounts of vitamin A are present in animal and fish livers and in fish-liver oils. Other rich sources are green leafy vegetables, green peas and beans, yellow vegetables containing carotene, milk, and eggs.

Bile is essential for the absorption and utilization of carotene, and any condition which excludes bile from the intestine prevents the conversion of carotene to vitamin A but apparently does not interfere with the absorption of vitamin A itself.

The most conspicuous ill effects of vitamin A deficiency are changes in *epithelial tissues* in general—chiefly epithelial trophy and desquamation followed by keratinization.

Its importance in surgical patients is not known, although it may play a part in maintaining normal hepatic function. Severe hepatic damage is associated with abnormally low levels of vitamin A. The importance of this vitamin in wound healing has also been suggested by experimental studies in which an acceleration of wound healing was observed after administration of moderate doses.

B. VITAMIN B COMPLEX

Vitamin B_1 (Thiamine). Thiamine is the first of the many vitamins collectively included in the term "vitamin B complex." Of the others, more is known of riboflavin and nicotinic acid. All three of these vitamins are concerned with the metabolism of carbohydrate as well as with maintenance of normal gastrointestinal function.

Thiamine deficiency may be precipitated in malnourished and dehydrated patients shortly after the start of intravenous injections of glucose, particularly when there is persistent vomiting or diarrhea, and fever. This is explained by the fact that thiamine is required for the metabolism of glucose, whose sudden introduction quickly depletes the low thiamine stores in the body of any malnourished patient and produces clinical signs of deficiency.

Clinical Manifestations of Thiamine Deficiency. The earliest manifestations of thiamine deficiency are really nonspecific; however, more pronounced manifestations are the classic signs and symptoms of polyneuritis.

Amount of Thiamine Required. A minimum of 0.3 to 0.5 mg. of thiamine appears to be required for the metabolism of 1,000 calories. *About 1.5 mg. should, therefore, be adequate for the daily quota. In patients with a deficiency, as much as 10 mg. a day should probably be given for a few days.* Overdosage is apparently without deleterious effect. Thiamine is much more stable than vitamin C and may be added to glucose or saline solutions with safety. On the other hand, it apparently cannot be added to solutions of amino acids because of chemical incompatibility. When amino acids are given, a separate injection of thiamine must be made.

Vitamin B_2 (Riboflavin). The available evidence suggests that this vitamin, with phosphoric acid and a protein carrier, forms the yellow enzyme of Warburg, which plays an important part in biological oxidation and reduction mechanisms and, therefore, in cell respiration.

Riboflavin and *nicotinic acid* have similar functions to that of thiamine in maintaining normal carbohydrate metabolism. Many preparations for thiamine for injection also contain these two associated vitamins. The daily requirement for riboflavin is usually set at 1 to 2 mg. and for nicotinic acid, at about 25 mg. The requirements are probably greater in the presence of fever, persistent vomiting, or diarrhea, and possibly also after operation. The usual amounts of riboflavin and nicotinic acid included for daily parenteral injections are 2 and 50 mg., respectively.

To insure an adequate supply of the entire vitamin B complex, Jolliffe advises the daily administration of one of the following: 20 gm. of Vegex, 60 gm. of brewers' yeast, or 30 gm. of aqueous liver extract.

Vitamin B_1 is given as thiamine hydrocloride, 50 to 200 mg. daily at first, preferably in two doses injected intramuscularly. After saturation, which may be recognized by the detection of a distinct odor resembling burnt rubber in the urine, the dose may be reduced to 10 mg. daily.

Nicotinic acid is given for the treatment of pellagra in doses of 500 mg. per day by mouth, or 50 to 80 mg. parenterally.

Riboflavin is given in doses of 3 to 5 mg. per day.

C. VITAMIN C

Vitamin C (ascorbic acid, cevitamic acid), which prevents scurvy, cannot be synthesized in the body. The daily requirement of vitamin C for man is from 28 to 100 mg. The blood contains normally 0.7 to 1.4 mg. per 100 cc. The richest food sources of vitamin C are the citrus fruits and the green leafy vegetables.

The basic physiological role of vitamin C is the promotion of normal production and maintenance of the *intercellular connecting or cement substances* of the supporting tissues of the body, particularly collagen. The fundamental pathological change resulting from an inadequate amount of this vitamin is a defect in this intercellular substance.

The *hemorrhagic tendency* in severe vitamin C deficiency, manifested first by capillary fragility, is attributed to weakening of the intercellular structure of the blood vessel walls. *Wound healing is promoted by vitamin*

C; a deficiency impairs the production and maintenance of the intercellular substance related to the growth of fibroblasts.

The best *test for vitamin C deficiency* is the determination of the *vitamin C concentration in the blood plasma* by titration; the test is accurate, rapid, and fairly simple.

In all patients in whom vitamin C deficiency exists preoperatively, the vitamin should be administered for a week or longer before operation to permit saturation of the tissues. The vitamin may be given by mouth in the form of fruit juices or as ascorbic acid tablets; it may be given intramuscularly, or sodium ascorbate may be given intravenously.

After operation on patients having a decreased vitamin C concentration in the plasma there occurs an immediate and marked drop of plasma vitamin C to still lower levels, yet the patients do not show clinical signs of scurvy, even though the plasma level of vitamin C reaches zero.

Lund and Crandon found that *plasma vitamin C determinations alone are not sufficient evidence on which to base treatment of surgical patients, as the great majority of patients with low levels are in no manifest danger due to the deficiency.* They recommend, however, that if there is a history of long-continued marked deficiency of intake of vitamin C, the patient being prepared for operation be given treatment (1 to 4 gm. of ascorbic acid daily).

Suggestive observations have also been made indicating that vitamin C may have a beneficial effect in experimental traumatic shock and hemorrhage, even when no deficiencies exist.

D. VITAMIN D

The richest natural source of vitamin D is fish-liver oils; the vitamin is also present in eggs, milk, fats, and some meats.

Vitamin D is soluble in fats, oils, ether, and alcohol but insoluble in water. Vitamin D belongs to the class of substances known as sterols or solid alcohols, such a *ergosterol.* The vitamin has been isolated in crystalline form and is called *calciferol.*

The chief metabolic significance of vitamin D lies in its relation to the metabolism of phosphorus and calcium.

(See section under metabolism of phosphorus and calcium for a more complete discussion of vitamin D.)

E. VITAMIN E

The tocopherols have been used for the treatment of fibrositis. (For a discussion of their use, see the bibliography.)

F. VITAMIN K

This is a *fat-soluble substance required for the formation of prothrombin,* which is an essential factor in the mechanism of coagulation of blood.

The chief function of vitamin K (Koagulations vitamin) lies in its utilization by the liver for the formation of plasma prothrombin.

1. Impaired Absorption. Bile acids appear to act as carrying agents for the passage of vitamin K across the intestinal wall, a function similar to that which they perform for vitamin D and carotene. Absorption from the

intestine is impaired in the absence of adequate amounts of bile (bile acids) in the intestine, as in obstructive jaundice and external bile fistula, with a consequent fall in plasma prothrombin and development of a hemorrhagic tendency. Adequate absorption in such circumstances follows administration of bile salts, the most effective of which appears to be sodium deoxycholate.

2. Hepatic Disease. The *liver is the chief, if not the only site of formation of plasma prothrombin,* and an adequately functioning liver is essential for the proper utilization of vitamin K in this process.

3. Demonstration of Vitamin K Deficiency. The methods employed for the demonstration of vitamin K deficiency consist in determination of the quantity of prothrombin in the plasma.

Decrease in prothrombin is evidenced by prolongation of the clotting time (prothrombin time) in these circumstances. Experience has shown that bleeding occurs commonly in patients with obstructive jaundice, bile fistula, and other conditions previously mentioned, when the plasma prothrombin concentration, as measured by these tests, falls below 30 to 40 percent of normal. Values of 40 to 70 percent of normal are potentially dangerous.

G. VITAMIN P

Vitamin P has been shown experimentally to enhance capillary permeability. (For a discussion of these experiments, see Best and Taylor.)

XIV. SULFONAMIDES

A. SULFANILAMIDE

1. Pharmacology. Sulfanilamide is a white, nearly odorless, crystalline compound. It has a slightly bitter taste. When administered by mouth, it is efficiently absorbed from the intestinal tract. Following the ingestion of a single large dose of the compound, an appreciable blood concentration is present within 1 hour and within 4 hours almost all of it has been absorbed. It diffuses rapidly to all tissues and fluids of the body. Lower concentrations are found in bone and fat than in other parts of the body.

From 10 to 15 percent of the sulfanilamide circulating in the blood is present as the conjugated or acetylated form, although the proportions vary in different individuals.

Over 90 percent of the absorbed sulfanilamide is excreted in the urine as the free and conjugated compounds. Excretion by the kidneys is directly related to the rate of urine flow. After cessation of sulfanilamide therapy, most of the absorbed drug is excreted from the body within 48 hours.

2. Doses and Methods of Administration. The seriously ill patient will require a blood level of 10 to 15 mg. per 100 cc. To attain this level, usually 1 to 1½ gr. (0.065 to 0.098 gm.) per pound of body weight is required during the first 24 hours of treatment. From one-third to one-half the calculated 24-hour dose should be given as an initial dose in order to attain an adequate concentration as soon as possible. The remainder is then given in divided doses every 4 hours. With progressive improvement, the doses of sulfanilamide are gradually reduced and given less frequently, that is, three to four times a day.

Whenever possible, the drug should be given by mouth.

Sulfanilamide may be given parenterally, and the subcutaneous route is preferable, using a 1 percent solution.

Bicarbonate of soda or lactate solution is definitely indicated when there is evidence of acidosis.

B. SULFAPYRIDINE

1. Pharmacology. Sulfapyridine is a white, odorless, practically tasteless, crystalline compound. Because of its insolubility, it is absorbed erratically from the intestinal tract. After a single oral dose, the maximum concentration in the blood is usually reached within 5 to 6 hours. The compound diffuses through the body fluids and tissues. The concentration in the cerebrospinal fluid is about 65 percent of that in the blood. There is a greater tendency for the body to acetylate sulfapyridine than is true for sulfanilamide. In some persons as much as 60 to 75 percent of the circulating sulfapyridine may be present as the acetylated product.

Sulfapyridine is excreted by the kidneys in much the same manner as sulfanilamide, though at a slower rate. When given orally, the amount recovered in the urine may vary from 30 to 60 percent of the ingested drug. Usually more of the drug is present in the urine as the acetylated than as the free form.

Six to eight hours after the initial injection, the optimal blood concentration of free sulfapyridine must be established by giving more of the compound.

Sulfapyridine has an additional pharmacologic mechanism not shared by sulfanilamide. Not infrequently it has a nonspecific antipyretic action. That is, following the administration of sulfapyridine, the temperature may quickly approach normal without any definite improvement in the patient's condition.

From a pharmacologic point of view, sulfapyridine is a less satisfactory drug to administer to patients than is sulfanilamide. It is more likely to induce severe nausea and vomiting. Its insolubility makes it more difficult to maintain desirable blood concentrations. There is a greater tendency for the human body to acetylate sulfapyridine. The acetylated form is highly insoluble, and its excretion by the kidneys may lead to serious urinary tract complications. On the other hand, sulfapyridine does not produce acidosis.

2. Doses and Methods of Administration. To maintain a blood level of 3 to 5 mg. of free sulfapyridine per 100 cc. in adults and older children, the usual procedure is to administer 3 to 4 gm. as an initial dose, followed by 1 gm. every 4 hours.

Sodium sulfapyridine may be injected directly into the venous circulation. It is usually administered as a 5-percent solution in sterile physiological saline solution or in distilled water.

C. SULFATHIAZOLE

1. Pharmacology. Sulfathiazole is a white, almost tasteless and odorless, crystalline compound. Sulfathiazole is readily absorbed when given by mouth. After a single large dose maximum blood concentrations are reached within 3 to 6 hours. It is also rapidly distributed in the tissues and body fluids, with the outstanding exception of the cerebrospinal fluid. Sulfathiazole is found in the spinal fluid in surprisingly low concentrations when compared to the blood levels.

A portion of the absorbed drug undergoes acetylation, slightly more than sulfanilamide and definitely less than sulfapyridine. The compound is rapidly excreted by the kidneys, in contrast to the slower rates of excretion of sulfanilamide and sulfapyridine. This property of sulfathiazole makes it more difficult to maintain elevated blood concentrations when doses equivalent to those for sulfanilamide and sulfapridine are given. From 80 to 90 percent of ingested sulfathiazole may be recovered in the urine within 24 to 36 hours. When the more soluble salt, sodium sulfathiazole, is given intravenously, practically all the injected compound may be recovered quantitatively in the urine. In general, less of the sulfathiazole than of sulfanilamide and sulfapyridine is present in the urine in the acetylated form.

Sulfathiazole has certain advantages over sulfapyridine. It induces less nausea and vomiting; it is more readily absorbed, and less of the compound is conjugated. However, sulfathiazole produces a higher incidence of drug fever, dermatitis, and renal complications than does either sulfanilamide or sulfapyridine.

2. Doses and Methods of Administration. Since the rate of absorption varies from individual to individual and the compound is excreted quite rapidly when compared with sulfanilamide and sulfapyridine, it is often difficult to maintain adequate blood concentrations. To attain blood levels comparable to those obtained with sulfanilamide and sulfapyridine, it is sometimes necessary to administer one and a half times the dose given for sulfanilamide and sulfapyridine. It may also become necessary to administer sulfathiazole at more frequent intervals to maintain a given concentration.

Sulfathiazole does not cause acidosis. There have been reports which suggest that equivalent doses of sodium bicarbonate may aid in preventing the precipitation of crystals.

D. SULFADIAZINE

1. Pharmacology. Sulfadiazine is a white, crystalline powder which is practically odorless and tasteless. Sulfadiazine is excreted slowly. Thus, from the point of view of absorption and excretion, sulfadiazine is like sulfapyridine. Once adequate blood and tissue sulfadiazine concentrations have been reached, they can be easily maintained in most cases.

After an initial oral dose, maximum blood concentrations are reached in 3 to 6 hours. In general, when sulfadiazine is administered by the oral route, adequate blood concentrations are reached only after the lapse of several hours. Sulfadiazine readily diffuses into pleural and ascitic fluids and exudates. There is some delay in the passage of sulfadiazine into the cerebrospinal fluid, but levels about two-thirds of those found in the blood are reached and sustained. About one-third of the sulfadiazine excreted in the urine is present in the conjugated form.

In summary, then, sulfadiazine is a compound that is well-tolerated, and, in the vast majority of patients, its administration is followed by fewer toxic manifestations than is sulfanilamide, sulfapyridine, and sulfathiazole. Adequate blood and tissue concentrations are readily maintained with sulfadiazine. The compound is bacteriostatically active against many species of micro-organisms.

2. Doses and Methods of Administration. Approximately the same

[illegible]

be obtained.

An *adult* weighing 100 pounds should receive an initial dose of 4 to 5 gm. and then 1 gm. every 4 hours. In the average case, the blood concentration will be around 15 mg. per 100 cc., though some variation will be encountered.

Children appear to tolerate sulfadiazine as well as adults. The initial doses are those described for adults. The 24-hour maintenance dose is of

0.15 to 0.2 gm. per kilogram, or about 0.065 to 0.1 gm. per pound of body weight This may be divided into four or six doses and given every 4 or 6 hours

E. SULFAGUANIDINE

1. Pharmacology. Sulfaguanidine is a white, crystalline powder, practically odorless and tasteless. It is not readily absorbed from the intestinal tract. Nevertheless when therapeutis doses are used in man, appreciable blood concentrations of the drug are obtained, with a portion of the compound present in the conjugated form. When the drug is absorbed, it apparently diffuses through the body, but it enters the spinal fluid less readily than sulfanilamide and sulfapyridine. The major portion of the absorbed drug is excreted in the urine, about 30 percent in the conjugated form. The toxic manifestations resulting from sulfaguanidine therapy are minimal. Occasionally a patient may complain of nausea and, less frequently, of vomiting. Drug fever, dermatitis, and conjunctivitis have been described. It is unusual to observe any effect on the hemoglobin or leukocyte levels.

Sulfaguanidine can only be administered orally.

F. SUCCINYLSULFATHIAZOLE

1. Pharmacology. Succinylsulfathiazole (sulfasuxidine) is a white crystalline compound that is very insoluble in water. From a therapeutic point of view, this drug is similar to sulfaguanidine. The drug is poorly absorbed when administered by mouth, and toxic reactions appear to occur less frequently than with sulfaguanidine.

G. SULFACETIMIDE

1. Pharmacology. Sulfacetimide is a white crystalline powder. It is odorless and has a slightly acid taste. It has essentially the same solubility as sulfanilamide. When given by mouth, it is rapidly absorbed and diffuses readily into the body fluids, including the cerebrospinal fluid. Sufacetimide is excreted through the kidneys and is eliminated rapidly. Sulfacetimide is said to be less toxic than sulfanilamide, though the manifestations recorded for sulfanilamide have been encountered in human subjects. Like sulfanilamide, it may cause acidosis.

It is administered only by the oral route. The compound has had a limited use, being particularly recommended for treatment of bacillary urinary tract infections. The usual daily intake of 4 gm. of sulfacetimide in divided doses will result in blood concentrations of 3 to 5 mg. per 100 cc. of the free form.

H. SULFAMERAZINE

1. Pharmacology. [illegible] ulfa- [illegible] iera- [illegible]. In comparison with sulfadiazine, sulfamerazine is more rapidly absorbed from the intestinal tract, more completely absorbed, and more slowly excreted in urine. The concentration in the cerebrospinal fluid is about 50 to 60 percent of that in the blood. Acetylation of sulfamerazine in the body approximates that following absorption of sulfadiazine.

The compound has been found to be effective in the treatment of pneumococcic infections, particularly pneumonia; hemolytic streptococcus diseases; urinary tract infections; and meningitis due to the influenza bacillus or the meningococcus.

2. Doses and Methods of Administration. In the treatment of severe infections in *adults* an initial oral dose of 3 to 4 gm. is given and then 1 gm. every 4 hours for 24 hours. At the end of this time, the blood concentrations are approximately 15 mg. per 100 cc.

The dose in severe infections in *children* that has been used with satisfactory results is approximately 0.05 gm. per pound of body weight, or around 1 gm. as the initial dose. The initial dose should not exceed 4 gm.

I. MODE OF ACTION

The primary action of the drugs is one of *bacteriostasis;* in other words, there is a diminution in the rate of growth of the bacterial cells. Under some conditions the drugs may actually kill small numbers of micro-organisms. *The compounds exert this antibacterial effect by interfering with the normal metabolism of the bacterial cell.* In the human body, the ultimate destruction of pathogens depends on two important factors: (1) The bacteriostatic action of the drug and (2) the defense mechanism of the host. The drug not only slows the rate of growth but injures the cell, permitting the normal defense mechanism to destroy the micro-organisms by such processes as phagocytosis and lysis.

There is no evidence that sulfanilamide or its derivatives interfere with the formation of antibodies, nor do they stimulate the production of immune substances.

The present concept of the mode of action of the sulfonamide compounds is that chemically related substances compete for a position in bacterial enzyme systems. Complex chemical reactions taking place in these enzyme systems are essential for growth. For the completion of one or more of these reactions, a substance like *paraaminobenzoic acid* is essential. Sulfanilamide may assume a place in the enzyme system because of its chemically related structure, but the reaction does not continue further; metabolism of the bacterial cell halts, and growth is impeded. In other words, *sulfanilamide blocks enzyme reactions essential for metabolism, whereas paraaminobenzoic acid completes the reactions and growth takes place.*

It has been demonstrated that different pathogens, once susceptible to the action of the sulfonamide compounds, may grow resistant to this action and grow freely in high concentrations of the drug.

J. ABSORPTION AND EXCRETION

All the sulfonamide compounds under discussion may be effectively administered orally. Because of differences in solubility, there are variations in the absorption of the drugs. *Absorption for the most part takes place in the upper part of the small intestine.* When clinical conditions prevail that preclude oral therapy, the drugs may be injected parenterally. The sodium salts of sulfapyridine, sulfathiazole, and sulfadiazine may be given by the intravenous and subcutaneous routes.

The kidneys serve as the major excretory channel for the absorbed drugs. Although the rate of excretion varies with the different compounds, it is relatively rapid. Considerable caution must be exercised in prescribing the sulfonamide compounds for patients with impaired renal function. When toxic manifestations arise from the drugs, liberal amounts of fluids will aid in eliminating them from the body. The fluid balance of the patient should be maintained so that a normal state of hydration exists.

K. TOXIC MANIFESTATIONS

The pathogenesis of the drug reactions is not clearly understood. It is difficult to differentiate the manifestations on a purely toxic basis or on the basis of temporary or permanent drug hypersensitivity.

In general, the initial reactions caused by a sulfonamide compound occur only after the drug has been taken for several days. However, on a subsequent occasion, a violent reaction may be precipitated immediately after a single small dose of the compound is administered. Persons may frequently become sensitive to one of the compounds and yet tolerate the other compounds without difficulty. In some persons, the acquired hypersensitivity to the sulfonamide compounds appears to be permanent.

Reactions have been most frequently encountered following therapy with sulfanilamide, sulfapyridine, and sulfathiazole. Fewer reactions occur following sulfadiazine administration.

In human beings, sulfanilamide has been the direct cause of a fatal outcome in some instances, death being due to agranulocytosis, hemolytic anemia, or acute necrosis of the liver. Most of the recorded fatal cases have been due to sulfapyridine and sulfathiazole, and the *outstanding pathological feature* has been the *renal damage.*

1. Cyanosis. Most patients receiving sulfanilamide in doses usually employed for systemic infections exhibit cyanosis of the skin and mucous membranes. This morbid appearance is due to methemoglobin and, in rare cases, to sulfhemoglobin. The cyanosis usually appears early in the course of treatment, and it is *not an indication for discontinuing therapy.* The formation of methemoglobin from hemoglobin is a reversible phenomenon, and methemoglobinemia disappears shortly after drug therapy is stopped.

2. Central and Peripheral Nervous System Manifestations. The sulfonamide compounds are said to have caused the following manifestations: Dysmorphopsia, aphasia, agraphia, stammering, toxic psychosis, peripheral neuritis, encephalomyelitis, myelitis, optic neuritis, transitory myopia, meningeal signs, blindness, and convulsions.

a. Nausea, Vomiting, and Diarrhea. After ingestion of the sulfonamide compounds, a number of patients complain of varying degrees of nausea. A smaller proportion have emeses. These disturbances are not uncommonly encountered after a large initial dose of the drug is taken. When lesser quantities are prescribed subsequently, the distress often diminishes. Generally speaking, serious nausea and vomiting are observed most frequently in patients taking sulfapyridine.

The foregoing effects of sulfanilamide and its derivatives originate in the central nervous system, although local factors may possibly play a role.

b. Headache, Dizziness, and Tinnitus. These manifestations occur

rather frequently in patients receiving any one of these drugs. Of the drugs that are readily absorbed from the intestinal tract, the incidence is probably less with sulfadiazine.

c. Mental Aberrations. At times, a patient's reactions may simulate alcoholic intoxication. Mental depression is observed commonly, as well as a diminution in mental acuity.

d. Peripheral Neuritis. Peripheral neuritis is a comparatively rare manifestation of sulfonamide toxicity.

3. Acidosis. In patients receiving *sulfanilamide* there is a *decrease* in the *carbon dioxide combining power of the blood.* Sulfathiazole, sulfapyridine, sulfadiazine, sulfaguanidine, and succinylsulfathiazole do not cause acidosis.

4. Drug Fever. Febrile reactions are frequently encountered in patients receiving the sulfonamide compounds. Drug fever has been seen more often in patients taking sulfanilamide and sulfathiazole than in those receiving sulfapyridine and sulfadiazine. Sulfathiazole is particularly likely to cause drug fever. Drug fever usually appears after a compound has been given for 5 to 10 days, occurring as early as the third day and, at times, after 14 to 21 days. A rise in temperature may occur after therapy has been discontinued.

Once a person has had drug fever, it may recur months later following a single small dose of the compound.

When drug fever is recognized, chemotherapy should be discontinued and copius amounts of fluid administered.

5. Skin Eruptions. Various types of skin reactions accompany sulfonamide therapy. *The lesions differ in their morphology.* Sulfanilamide has been a common incitant, and the types of lesions have been described as *erythematous, morbilliform, maculopapular, erythema-multiforme-like, vesicular, bulbous, urticarial, exfoliative, and purpuric.* A type of eruption commonly observed in patients receiving sulfathiazole is a red nodular lesion appearing on the anterior aspects of the lower extremities and frequently involving the skin of all extremities. This lesion may make its first appearance around the elbows, fingers, and knees. The eruption has been observed on the palms of the hands. It has the appearance of erythema nodosum.

Skin eruptions usually appear after the drug has been given for 5 to 7 days. They may occur earlier or much later.

Drug therapy should be suspended at once when a skin eruption becomes apparent.

6. Jaundice and Hepatic Damage. Sulfanilamide occasionally causes varying degrees of liver damage in human beings. Although in some instances jaundice appearing in patients receiving sulfanilamide may be directly due to destruction of erythrocytes by the drug, in a broad sense any evidence of jaundice must be looked on as evidence of relative liver dysfunction.

If hepatitis does appear while a patient is receiving sulfanilamide, therapy should be discontinued and a diet prescribed high in carbohydrate and protein but low in fat content.

7. Anemia. Sulfonamide therapy is often accompanied with varying gradations of anemia. The decline in hemoglobin content and erythrocytes may manifest itself a few days after beginning treatment. Beginning with the second or third day of therapy, the anemia progresses. Anemia is likely to occur with increasing severity as treatment is prolonged. *The true incidence of sudfanilamide-induced anemia is probably below 10 percent.* It is seen more frequently in children than in adults.

Occasionally, patients exhibit an acute type of hemolytic anemia.

Moderately severe anemias may be adequately treated by frequent blood transfusions if it is imperative that drug therapy be continued. Iron may be prescribed in the form of ferrous sulfate. When an acute hemolytic anemia appears, chemotherapy must be discontinued at once and transfusions should be given to correct the anemia.

8. Leukopenia, Granulopenia, and Agranulocytosis. Depression of the level of white blood cells occurs much less frequently than a reduction in the number of red blood cells following sulfonamide therapy. *A lowering of the white blood cell count induced by the drugs usually occur after a compound has been given for a considerable period.*

The most serious complication is malignant neutropenia terminating in fatal agranulocytosis. When treatment is carried on beyond two weeks, the leukocyte levels must be followed closely. *Chemotherapy must be stopped if the level falls below 3,500 to 4,000 cells per cubic centimeter.*

Sulfanilamide and sulfapyridine both cause leukopenia and neutropenia. They are rarely encountered with sulfathiazole.

When malignant neutropenia appears, sulfonamide therapy must be discontinued at once. *Specific treatment calls for the administration of pentnucleotide and perhaps yellow bone marrow.*

9. Complications of the Urinary Tract. Sulfanilamide rarely causes complications of the urinary tract. The responsible drugs are sulfapyridine, sulfathiazole, and sulfadiazine.

Perhaps the commonest mechanism responsible for urinary tract complications is the result of the precipitation of sulfonamide crystals either in the renal tubules or in the renal pelves and ureters. In other words, *mechanical interference* with the flow of urine must be regarded as the most frequent source of renal failure or symptoms and signs referable to the urinary tract.

The sulfonamide compounds may interfere with renal function or produce signs and symptoms referable to the urinary tract in three ways. First, in the course of an acute attack of hemolytic anemia caused by one of the drugs, especially sulfanilamide, renal failure may be encountered. Second, the sulfonamide compounds may have a direct toxic effect on the renal parenchyma. Third, crystalline sulfonamide material may be precipitated in the kidney or along the urinary tract, resulting in a mechanical interference with the flow of urine.

The treatment of urinary tract complications is related to the severity of the condition. *Gross hematuria calls for prompt cessation of sulfonamide therapy.* This also applies to pain of renal or ureteral origin. *The appearance of sulfonamide crystals in the urinary sediment is not a contraindication to continuation of sulfonamide therapy.* One of the earliest manifestations

of disturbances taking place in the kidney or lower urinary tract is a diminution in the total amount of urine excreted in a 24-hour period. In these circumstances, drug therapy should be terminated and fluids administered so that the total urinary output is 1,000 to 1,500 cc. per 24 hours.

The appearance of sulfonamide crystals in urine is frequently encountered and is not an indication of impending renal complications, nor, as stated previously, is it sufficient indication to discontinue chemotherapy.

10. Painful Joints. An unusual type of reaction accompanying especally sulfathiazole therapy is a sudden onset of pain in the larger joints. The overlying skin may be reddened and swollen. One or more joints may be involved.

11. Conjunctivitis and Scleritis. Another extraordinary toxic manifestation arising as a result of sulfathiazole therapy is an inflammatory reaction of the bulbar conjunctivas and scleras. This usually appears after treatment has been continued for several days.

XV. PENICILLIN

The Oxford unit as an international unit contains 0.0006 mg. of pure crystalline sodium salt of penicillin II which is to be maintained as a standard at the National Institute of Medical Research.

A. MORPHOLOGICAL CHANGES IN BACTERIA EXPOSED TO PENICILLIN

Penicillin apparently acts on bacteria only in the growing phase and fails to have a bactericidal action when conditions are such that the organism cannot grow. Gardner was the first to point out that under the influence of sublethal concentrations of penicillin the bacteria lose their regular form. What is normally a short bacillus may become a long thread and cocci may take on a swollen and bloated appearance.

B. GENERAL RULES FOR PENICILLIN TREATMENT

Penicillin should be used only when there is an infection by a penicillin-sensitive organism. The following list shows the sensitivity of the commoner microbes.

Sensitive

- Staphylococcus
- *Streptococcus pyogenes*
- *Streptococcus viridans*
- Some anaerobic streptococci
- Pneumococcus
- Gonococcus
- Meningococcus
- *Neisseria catarrhalis*
- Micrococcus
- Sarcina
- Actinomyces
- *B. anthracis*
- Hay bacillus (*B Subtilis*)
- Diphtheria group
- Clostridia (*tetani, welchii, septique, botulinum,* etc.)
- *Streptobacillus moniliformis*
- *Erysipelothrix rhusiopathiae* (erysipeloid; swine erysipelas)
- *Spirillum minus* (rat-bite fever)
- Spirochetes of—
  - relapsing fever
  - syphilis
  - yaws
  - Vincent's agina
  - Weil's disease
- Larger viruses (psittacosis, ornithosis)—partly
- Rickettsia—partly

Insensitive

- Enterococcus (*Streptococcus faecalis*)
- Nonpathogenic gram-negative cocci
- Typhoid-coli-dysentery group
- *Vibrio cholerae*
- *Proteus*
- Pseudomonas group (*Ps. aeruginosa, B. fluorescens*)
- Hemophilus group (*H. influenzae, H. pertussis*)
- Acid-fast group (tubercle, smegma, etc.)
- Pasteurella group (*P. pestis, etc.*)
- Brucella
- Friedländer's bacillus (*Klebsiella pneumoniae*)
- Most of the viruses
- Yeasts
- Monilia
- Molds

In most cases, there is a broad line of distinction between the sensitive and insensitive microbes, and, while success can be looked for in the treatment of infections by those listed as sensitive, failure is more than probable when the microbe is in the insensitive list.

Penicillin must be administered in such a way that it comes in contact with the infecting organism.

The dose should be such that in the infected area the concentration of penicillin is sufficient to destroy the bacteria. In systemic treatment the dosage can be controlled by estimations of the blood concentration. After an injection there is a rapid rise in the concentration of penicillin in the blood; some is excreted and some diffuses into the tissues; then as the blood concentration falls below that of the tissues, it returns from the tissues to the blood.

It is, fortunately, not so easy to make organisms resistant to penicillin as it is with the sulfonamides and it has been shown that in the case of some microbes at least this fastness is only temporary.

The treatment should be persisted in until the infection is defeated.

C. COMBINATION OF PENICILLIN WITH SULFONAMIDES

The combination of a sulfonamide with penicillin has been extensively used in practice, and, apart from the possible toxic effects of the sulfonamide, there does not seem to be any reason why they should not be combined in infections which are susceptible to both. *They act on the microbe in a quite different manner. Paraaminobenzoic acid, which neutralizes sulfonamide action, has no such effect on penicillin, and microbes which have been rendered sulfonamide fast are still fully sensitive to penicillin and vice versa.*

D. LIMITATIONS OF PENICILLIN TREATMENT

1. Infections With Insensitive Organisms.

2. Sequestered infections. Sometimes the infecting bacteria exists in situations sequestered from the blood stream, as in sequestra in chronic osteomyelitis. The surrounding blood and tissues may be saturated with penicillin and, theoretically, if this is maintained for a sufficient length of time, the penicillin might diffuse in and destroy the infection. This is often impracticable, however, and surgery must be combined with penicillin treatment.

3. Penicillinase. A considerable number of bacteria produce in their growth a substance, penicillinase, which destroys penicillin. Some of these, especially coliform bacilli, are found in infections in association with penicillin-sensitive organisms In such cases the penicillinase produced may definitely militate against the success of penicillin treatment, which otherwise would be effective.

E. PROPERTIES OF PENICILLIN

1. Penicillin is highly bactericidal to certain organisms in their growing phase. The organisms swell and lyse. It is specific in its action, being ineffective against certain organisms, mainly gram-negative ones.

2. Its activity is maintained in the presence of blood, serum, pus, and large numbers of bacteria; it does not injure leukocytes and is nontoxic, both locally and systemically.

3. It is rapidly excreted into the urine, and it is necessary, therefore, by various devices, to maintain its concentration during treatment.

4. It is thermolabile, its thermostability being maximal when the substance is dry and minimal when water or moisture is present. The sodium salt is very hygroscopic and more liable to decompose during storage than the calcium salt. The calcium salt is more suitable in the manufacture of dry preparations of penicillin, such as tablets and lamellae and for insufflation powders.

5. Whereas aqueous solutions of penicillin are unstable, oily suspensions of the dry substance are relatively stable.

6. Acids or alkalis decompose it. The optimum pH for stability in aqueous solution is 6 to 6.5, while a practical range is about pH 5.5 to pH 7.5.

7. Certain heavy metallic ions, such as copper, lead, mercury, and silver, tend to decompose penicillin, and contamination from these metals must be avoided in the preparation of aqueous solutions. Their effect may be negligible in oily or fatty media. Oxidizing agents cause decomposition.

8. Penicillin is quickly inactivated by the enzyme penicillinase which is excreted by certain bacteria when growing in aqueous solutions of penicillin. Penicillinase has the stability and reactions of enzymes and is destroyed in aqueous solution by boiling for 10 minutes. It is unlikely to be produced by bacteria in oily media. Nonsterile samples of distilled water may contain penicillinase, and, if such water is used for the preparation of penicillin solution, it must be previously boiled and cooled to destroy any enzyme present.

9. Certain pathogenic bacteria may develop resistance to penicillin. This can occur during clinical treatment with the drug. Underdosage may be a contributory factor, and, therefore, it is important that penicillin preparations of doubtful potency should not be used.

Stability and Storage. The most important factor influencing the stability of penicillin is water or moisture, the presence of which increases the effects of heat and pH. Moreover, decomposition by penicillinase can occur only in the presence of water. Therefore great care should be taken that moisture is not admitted when resealing a container of penicillin after removal of some of its contents. This is particularly important with the sodium salt.

Compatibility of Penicillin. It is compatible with the sulfonamides when mixed as dry powders, but it is inactivated rapidly in aqueous solutions of the sodium compounds of the sulfonamides because of their alkalinity.

It is not inactivated by certain antiseptics which are useful adjuncts in aqueous preparations of penicillin to inhibit the development of microorganisms insensitive to penicillin, including those which produce penicillinase.

F. PHARMACOLOGY OF PENICILLIN

The behavior of penicillin in the body differs from that of the sul mides in several ways; two are fundamental and account for the far gr difficulty of its administration. The first of these difficulties is its insta in acid solution, which results in the loss of the greater part of any administered by mouth. This obstacle can be overcome by some fo parenteral injection, which is readily accomplished, since penicillin is h soluble, innocuous to any tissue even in concentrated solution, and qu absorbed into the circulation. The second and more serious difficu that, whereas the renal excretion of sulfonamides is relatively slow, th penicillin is exceedingly rapid. An initial concentration in the blood, greater than that necessary for therapeutic effect, falls steeply, sinking the therapeutic level within about 3 hours after a conventional dos been given. In order to overcome most infections which are treated penicillin, it is necessary to maintain a therapeutic level in the blo concentration, that is, which will inhibit the growth of the respo micro-organism—for at least several days and often for a week or 10 Treatment in exceptional circumstances must be even more prol than this, but whatever the duration, its effect must be continuous a therapeutic blood level must be maintained at night as well as durin day.

1. Administration.

a. Intermittent Injection. Three routes are possible for intermitte jection: (1) The intravenous route, which produces a maximum blood immediately; (2) the intramuscular route, which produces a maxi blood level within a few minutes; (3) the subcutaneous route, wh followed by rather slower absorption. Penicillin is, therfore, rapidl sorbed into the circulation. If all the drug remained there, the do quired to produce a therapeutic concentration in the blood adequat many purposes—for example, 0.05 unit per milliliter—in an adult of av weight would be only 350 units. But renal excretion is rapid, and to pensate for this rapid wastage it is necessary to give at least 50 this amount.

It appears that the capacity of the normal kidney to excrete peni is unlimited for practical purposes; hence a *cumulative effect cann achieved.*

b. Continuous Infusion. Continuous infusion of penicillin solution constant rate, whether intravenous or intramuscular, maintains a con level in the blood.

2. Distribution in the Body. A large proportion of the quantity ad istered appears in the urine, and penicillin is also readily detected ir bile for several hours; a small amount is found in the saliva, but nor the cerebrospinal fluid, lacrimal secretion, or pancreatic juice. Penic traverses the placenta; it has been demonstrated in the fetal circula when a large dose has been given to the mother shortly before the birth.

Diffusion takes place from the blood into serous sacs. Diffusior penicillin is rapid from a normal serous cavity, but slow from such a col tion as an empyema, in which an effective concentration may persist

several days. Absorption from a serous cavity is retarded if penicillin is being administered systemically at the same time.

The inability of penicillin to pass into the *cerebrospinal fluid* is by far the most important gap in its distribution in the body. The intrathecal injection of penicillin solution is safe and highly effective. A single dose of 4,000 units will maintain an adequate level in the cerebrospinal fluid for 24 hours. It should be noted that, although intrathecal injection is imperative for the treatment of meningitis, infective processes in the substance of the brain and cord can be attacked through the circulation. The successful treatment of neurosyphilis by intramuscular injection is evidence of this.

Not all the penicillin administered by any route can be accounted for. Rather more than half is excreted in the urine and some must be lost in the bile, but a certain proportion, probably about 30 percent, disappears.

3. Renal Excretion. About 60 percent of the parenterally injected penicillin is excreted in the urine. The greater part of an intravenous or intramuscular dose escapes in the first hour and diminishing quantities thereafter, a small amount still being found several hours after it has ceased to be detectable in the blood. The concentration attained in the urine is high.

Excretion is tubular and can be retarded by the simultaneous administration of certain other substances which are excreted by the tubules, such as paraaminohippuric acid. It is also retarded by nephritis and other lesions impairing renal function.

4. Prolongation of Therapeutic Effect. *Several methods of achieving this have been proposed, all of which act in one of two ways: They either obstruct renal excretion or bring about slower absorption from the site of injection.*

a. Delayed Excretion. Excretion by the healthy kidney can be delayed by administering certain other substances which are excreted *via* the tubules.

b. Delayed Absorption. When a solution of penicillin is injected intramuscularly, the greater part of it is absorbed within a few minutes. If this process could be retarded, a continuous and prolonged moderate blood level should result, instead of a sharp rise to a high level followed by a rapid fall. Undoubtedly the most effective means of retarding the process is to suspend finely pulverized solid penicillin in oil, as first suggested by Romansky and Rittman, who devised it for the treatment of gonorrhoea by a single injection. The improved preparation now in use contains 300,000 units of highly purified calcium penicillin (potency about 1,000 units per mg.) in 1 ml. of peanut oil containing 4.8 percent of beeswax. The subcutaneous injection of 1 ml. of this compound maintains an assayable blood level for 20 hours in the majority of patients.

c. Oral Administration. It now seems that oral administration of about five times the intramuscular dose will usually produce the same effect.

Oral administration is therefore perfectly feasible if expenditure at the rate of, for example, 600,000 units a day is justified. Finland takes the view that it should be used only in infections due to highly sensitive organisms. He would not include even staphylococcic infections in this category and adds that very severe infections of any kind call for treatment by the more dependable parenteral route.

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ment of bacteria in cultures which otherwise would be inhibited by the penicillin contained in the material.

It causes trouble in penicillin therapy in two ways: (1) If penicillinase-producing bacteria are present in sufficient numbers in a lesion associated with penicillin-sensitive organisms, the latter may be protected by the penicillinase; (2) *if a penicillinase producer contaminates a penicillin preparatoin (solution or cream) it can rapidly destroy its activity.*

5. Toxic Effects. For all practical purposes, penicillin of good quality has no toxicity at all. *Those that do occur are all of a minor nature.* There is no recorded instance of any damaging effect on the bone marrow, liver, kidney, or other organs which may be affected by chemotherapeutic agents of other kinds.

One of the first toxic manifestations to be observed was *thrombophlebitis* resulting from continuous intravenous infusion, necessitating frequent change of vein. This appears to have been due mainly to *impurities.*

Treatment with certain batches of penicillin for several days can cause *fever.* There is no need to discontinue treatment if the continuation of treatment is considered necessary. Fever of this kind occurs commonly during administration by continuous intramuscular infusion and is associated with inflammatory changes at the site of injection, particularly when this site is not changed every 2 days, as it should be. A purulent or semipurulent effusion may form and although the pus sometimes contains a penicillin-resistant organism such as *Ps. aeruginosa*—in which case the explanation is obvious—oftener than not it is sterile. In such cases the continued infusion at one site of a concentrated solution of perhaps not highly purified penicillin presumably causes chemical damage to the tissues.

The most sensitive tissues to inferior penicillin are those of the central *nervous system,* and *meningeal irritation,* evidenced by a cerebrospinal fluid pleocytosis, has been frequently described following intrathecal injection. Such an effect should not deter further treatment if it is vital to continue it. The purer penicillin of the present day is relatively free from this disadvantage, and larger doses are being given with impunity.

Sensitization phenomena. Urticaria has been observed fairly often and may occur at any stage of treatment. Various other skin conditions have been described, and a dermatitis may also follow local application. When such manifestations occur at a late stage in treatment, or particularly during a second course, it is natural to suspect that the patient has become sensitized.

6. Estimation of Penicillin Sensitivity of Infecting Organism. There are many methods of testing the sensitivity of a microbe, and the actual method used will depend on the circumstances. As with the test of the potency of penicillin, they fall into *two classes: A serial dilution method or a measure of the distance to which a culture is inhibited on an agar plate.* In both cases, if exact measurements are required, a control should be made with a standard culture of staphylococcus under exactly the same conditions.

G. PENICILLINASE

Abraham and Chain found that certain penicillin-insensitive organisms contained a substance—having the properties of an enzyme—which destroyed penicillin. This substance they called penicillinase. Penicillinase can be extracted from the bodies of the organisms in a number of ways, but it can be more easily prepared by simple filtration of a week-old broth culture of a suitable microbe—generally a coliform bacillus or *B. subtilis.*

Penicillinase is useful in that it can be used to neutralize the bacteriostatic power of penicillin in blood, pus, or other fluid, and so allow the develop-

ment of bacteria in cultures which otherwise would be inhibited by the penicillin contained in the material.

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XVI. STREPTOMYCIN AND STREPTOTHRICIN

After administration of streptomycin and streptothricin, it is evident that the *toxicity* of these two substances *differs* in a number of respects. In contrast, the *antibacterial activity of streptomycin and of streptothricin are remarkably similar,* as shown by the fact that both antibiotics are mainly *active against gram-negative bacteria in vitro* and *in vivo.* Moreover, both agents inhibit the growth of some gram-positive species, as well as certain *acid-fact microorganisms,* including the human tubercle bacillus.

The behavior of the two drugs, with respect to absorption, excretion, and chemotherapeutic properties, appears to be almost identical.

A. DOSAGE

In general, *acute infections* may be treated with a total dose of 2 to 3 gm. daily given in divided doses 3 to 4 hours apart. In *chronic* infections a daily dose of 1 to 2 gm. may be sufficient to control the disease.

B. ABSORPTION

Following the parenteral injection of a single does of streptomycin, the drug concentration in the serum reaches a peak shortly after the injection and thereafter decreases at a uniform, but relatively rapid, rate, over a 2- to 6-hour period.

1. Repeated Parenteral Administration. Therapeutic drug concentrations can be maintained in the blood for at least 3 hours following injection of an adequate dose. By giving streptomycin or streptothricin every 3 hours by intramuscular injection, the blood concentration can be maintained at a therapeutic level, the latter depending upon the dose administered.

2. Continuous Parenteral Administration. The methods of continuous intravenous and intramuscular infusion have been employed with considerable success. Of the two procedures, the intramuscular infusion may prove to be the method of choice, since the desired blood concentrations may be obtained without the occurrence of certain untoward reactions, which are occasionally seen following rapid intravenous administration.

When 3.0 gm. of streptomycin, dissolved in 3,000 ccm. of a 5-percent *glucose solution, is administered daily by continuous intravenous infusion,* blood levels of streptomycin varying between 20 and 60 micrograms per cubic centimeter of blood have been obtained. Lower doses of 1.0 gm., by either the intravenous or intramuscular method, produces blood levels ranging between 10 and 20 micrograms of streptomycin per cubic centimeter of blood.

3. Oral Administration. When streptomycin is given by mouth to various animal species or to man, the drug concentration in the blood is low, even when relatively large doses are administered. The effective d

[illegible] 20 times as great as the parenteral dose, and these [illegible]

[illegible] tomycin remains in the spinal fluid for a long period of time.

5. Distribution of Streptomycin in Various Body Fluids. With few exceptions, streptomycin diffuses fairly rapidly into most body tissues, following parenteral administration.

6. Diffusion Into Cerebrospinal Fluid. *Diffusion of streptomycin into the cerebrospinal fluid does not take place readily. When high concentrations of streptomycin are desired in the cerebrospinal fluid, the drug must be given by the intrathecal route.*

7. Peritoneal Fluid. After parenteral administration streptomycin rapidly appears in the peritoneal fluid. Results show that streptomycin first appears in the peritoneal fluid one-half hour after drug administration.

8. Pleural Fluid. The appearance of streptomycin in pleural fluids appears to be somewhat slower than in the peritoneal fluid.

9. Fetal Blood and Amniotic Fluid. Streptomycin does enter the fetal circulation and the amniotic fluid.

C. EXCRETION

After parenteral administration, streptomycin and streptothricin are *readily eliminated from the body,* the major portion being excreted in the urine. Experimental studies show that approximately 50 to 80 percent of streptothricin or streptomycin can be accounted for by renal excretion. Streptomycin and streptothricin are rapidly eliminated from the body, provided fluid intake is adequate and renal function is normal. If renal function is impaired, as after the administration of streptothricin or, at times, with large doses of some lots of crude streptomycin, the drug accumulates in the body.

Quantitative studies on the rate of excretion of streptomycin and streptothricin show that most of the drug is excreted within the first 12 hours after the injection.

Excretion of streptomycin also occurs in the bile.

D. TOXICITY

Large doses of streptomycin for longer than 2 or 3 weeks not infrequently leads to toxic reactions of varying severity. The most frequent serious toxic reaction is *impairment of function of the vestibular portion of the eighth cranial nerve.* The occurrence of tinnitus is an indication for discontinuing therapy.

Decreased kidney function and even anuria have been reported and occur most frequently in patients with previous kidney damage.

Minor toxic reactions, including *pain* at the site of injection, *urticaria,* and other cutaneous rashes, are not infrequent following streptomycin therapy.

E. CHEMOTHERAPEUTIC ACTION

1. In Vitro Studies. Streptomycin and streptothricin in small quantities are bacteriostatic for a variety of *gram-negative and gram-positive bacteria.* In addition, the *tubercle bacillus* is sensitive to both substances.

2. Action in Vivo. In general, organisms which are sensitive to streptomycin or streptothricin *in vitro* are also sensitive *in vivo.*

Among the bacterial infections which respond to streptomycin and streptothricin therapy are those produced by most strains of *Escherichia coli, Salmonella schottmülleri, Salmonella aertrycke, Eberthella typhi,* and *Aerobacter aerogenes.*

3. Experimental Brucellosis. Studies in the infected chick embryo by Jones and in the guinea pig by Live and associates, suggest that streptomycin is an effective agent for the treatment of experimental infections due to *Brucella abortus.* The lesions produced in man and the experimental animal are not identical and, therefore, it is not possible to predict what influence streptomycin will have on brucellosis in man.

4. Experimental Tularemia. *Pasteurella tularensis* is extremely sensitive to streptomycin.

5. Experimental Tuberculosis. A final decision as to the probable value of this drug in tuberculosis cannot be made at the present time.

6. Experimental Infections Caused by Pseudomonas pyocyanea and Proteus. The efficacy of streptomycin or streptothricin against these organisms varies considerably with different strains. In general, however, both organisms are quite resistant to streptomycin and streptothricin and, in addition, have marked potentialities for acquiring resistance to these drugs.

7. Experimental Infections Due to Gram-Positive Bacteria

Cocci. Animals infected with *Staphylococcus aureus, Streptococcus hemolyticus,* and *Diplococcus pneumoniae* can be protected with large amounts of streptomycin.

Anaerobes. The group of anaerobic sporulating bacilli, including *Clostridium tetani, Cl. welchii, Cl. sordelli,* and *Cl. septique,* is quite resistant to the action of streptomycin and streptothricin.

Diptheria. Although *Corynebacterium diptheriae* and related species are quite sensitive to streptomycin *in vitro,* little is known about the influence of the drug on the organism *in vivo.*

Spirochetal Infections. Streptomycin has some effect on spirochetal infections, but this effect is considerably inferior to that of penicillin.

Fungi. In vitro tests show that streptothricin is much more active than streptomycin as a fungicide. Streptomycin has been reported to have no effect on *Histoplasma capsulatum.*

Protozoa. Streptothricin and streptomycin were not found active in experimental malaria, rat filariasis, or trypanosomiasis.

F. ACQUIRED RESISTANCE TO STREPTOMYCIN

Demerec postulates two possible mechanisms for the development of penicillin-resistant organisms, which might apply equally well to streptomycin: (1) Resistance is an acquired characteristic which develops through the interaction between bacteria and penicillin, when the two are in contact with each other; and (2) resistance is an inherited characteristic which originates through mutation, and its origin is independent of pencillin treatment. In either case, it is possible, with most organisms to

prevent the occurrence of fastness by exposing the organism to adequate bacteriostatic or bactericidal concentrations of the drug.

G. CONCLUSIONS

1. Streptomycin inhibits the growth of gram-negative and gram-positive pathogenic bacteria. The colon organisms and Friedlander's group are especially sensitive, while the Proteus, Aerogenes, and Pyocyaneus groups are more resistant to this drug.

2. Nonhemolytic streptococci and hemolytic staphylococci require four to eight times as much streptomycin to inhibit their growth when human blood, plasma, or serum is added to the medium.

3. Though there is no correlation of the sensitivity of organisms to penicillin and streptomycin, subinhibitive doses of each, when combined, have an additive effect.

4. To combat aerobic pathogenic bacteria of surgical infections, a sustained minimum blood concentration should be not less than 8 units per cubic centimeter. To accomplish this, 400,000 units of streptomycin should be given intramuscularly every 4 hours. In surgical infections, treatment should be continued for 7 days or longer; in genitourinary infections, for 3 days or longer.

5. Adequate surgery is important if streptomycin therapy is to succeed in eliminating infection when dead tissue, collections of pus, foreign bodies, calculi, and thick-walled sinus tracts are present.

6. Too small a dose, too short a course of treatment, or failure to evacuate pus, calculi, sequestra, or foreign bodies predispose to the prompt development of drug-fastness.



Orthopedic

I. BONE

True bone consists of calcareous material deposited in a fine matrix of collagenous fibers, and it varies considerably in its density. Bone is essentially a living tissue supplied with blood vessels and nerves and not only its external form but also its internal architecture can change in response to the stresses and strains to which it is subjected during life.

The primary function of bone is to serve as a supporting framework for the soft tissues. It also forms a series of mechanical levers, to which are attached muscles and ligaments. It also has a protective function and, in addition, serves as a reservoir for calcium.

A. STRUCTURE AND GENERAL FEATURES

If a limb bone, such as the femur, is sectioned longitudinally, the shaft is seen to be a tubular structure with walls of dense compact bone and a central cavity, the medullary or marrow cavity. The term cancellous bone is given to the extremities of the bone, which are filled with a sponge-work of bony trabeculae in the interstices of which is yellow marrow mixed with red marrow. The cancellous tissue at the extremity of a long bone is covered on the surface by a relatively thin shell of compact bone. The bony trabeculae which compose cancellous tissue are arranged and determined by mechanical and growth factors. About 60 percent of the weight of compact bone is formed by inorganic material, consisting almost entirely of calcium phosphate. This salt is deposited in a fibrillary basis of collagenous tissue. The calcified matrix forms the interstitial substance of bone. This substance is arranged in thin lamellae, is perforated by fine canals containing blood vessels and nerves, and is also richly permeated with bone cells (osteocytes). The lamellae are arranged in concentric rings around the fine canals which penetrate the bone everywhere. These are the Haversian canals. Each canal and its series of encircling lamellae comprise what is called a Haversian system. Between the lamellae are minute oval cavities—lacunae—from which extend on all sides fine branching canaliculi. There seems to be little or no anastomosing of canaliculi of one Haversian system and those of an adjacent system. Each lacuna is completely occupied by an osteocyte, and these bone cells, in turn, communicate through the canaliculi to neighboring cells by means of fine protoplasmic processes.

A more detailed description of the structure of bone follows.

1. Histology

a. Coarse-Fibered or Primary Bone. There are essentially two types of bone, depending on the arrangement and character of the collagen fibers. The characteristic bone of the skeleton of the human fetus and newborn is mainly coarse and the fibers are irregular. This type of bone practically disappears by the fourth year of life and is replaced by typical adult bone, which has for its distinguishing characteristic fine fibers in lamellar arrangement. Phylogenetically, coarse-fibered bone is older and more primitive; it is the type of bone generally seen in ossified fibrous tumors and osteogenic sarcoma and is the first bone formed in the repair of a lesion of bone even in an adult. As a general rule, whenever new bone is being formed, except in the case of normal reconstruction that goes on constantly in lamellar bone, it is first formed as fiber bone, which may later be replaced by lamellar bone.

When bone is first formed in the fetus, either as membranous or as endochondral bone, it consists of trabeculae containing course fibers and cells and lies between a loose vascular connective tissue. The coarser fibers of primary bone are better known as Sharpey fibers; they are present in great numbers in the fetus and newborn and in small numbers in the adult. They are derived from the periosteum. The part that the osteoblasts play in the formation of fiber bone is controversial. Many authorities believe that all the embryonal primary bone is of osteoblastic origin.

b. Fine-Fibered, or Lamellar Bone. When an adult tubular bone is sawed open longitudinally, parts of it are seen to be dense and compact in texture and other parts spongy. Accordingly, two forms of adult osseous tissue are distinguishable, compact and spongy bone. The difference between them depends in part on the different amounts of calcified tissue in proportion to the size and number of open spaces in the bone. In all bones, the outer portion is compart and the spongy bone is contained within.

(1) *Compacta* A cross-section of the cortex of a bone shows that there are several ways in which the lamellae are arranged in the compacta. Some are deposited about blood vessels, as the Haversian lamellae, to form the Haversian systems. Others do not surround blood vessels but are deposited by periosteum or endosteum and are known as the outer and inner concentric, or ground, lamellae.

Interstitial lamellae fill in the spaces between the Haversian systems.

A system of preformed *canals* in the cortex carries blood through the compacta. These canals are known as the Haversian canals, Schwalbe's canals, and the communicating canals, depending upon their direction and site in the lamellae.

The *Haversian system* constitutes the basic structural unit of lamellar bone. The osteoblasts deposit the Haversian lamellae in layers on the coarse-fibered bone about the walls of the blood vessels in the primary marrow spaces, thus forming the first Haversian systems. The replacement of coarse-fibered bone by lamellar bone occurs in the following manner: Osteoblasts about the vessel deposit a layer of osseous material on the fiber bone, forming a cylinder which is known as a Haversian lamella. The material is deposited on the fiber bone by a process of substitution. Lamellar

bone formed about the vessel probably grows centrifugally and centripetally. The lamellae about the Haversian canals are disposed in a ringlike manner, but sometimes, when one canal is anastomosing with another, they do not extend entirely around the canal. In general, it may be said that the widest Haversian canals are surrounded by the fewest lamellae and the medium-sized canals by the most lamellae.

The lamellae are traversed by the canaliculi and processes of the *bone cells,* whereas the lacunae, containing the bone cells, are either in the lamellae near the borders or between two lamellae. The lacunae are minute recesses in bone, from which extend fine tubes, called canaliculi. The canaliculi pass across the lamellae and communicate with the canaliculi of the neighboring lacunae so as to connect the lacunae with one another. It is probable that the chief purpose of these minute passages is to convey nutrient fluid from the Haversian canals through the mass of hard bone that lies around and between them. Each lacuna is occupied by a nucleated bone cell.

Each *lamella* consists of many fibrils embedded in a cement substance, with calcium salts impregnated between fibrils. Together these elements constitute the *ground substance* of the bone. It is believed that the inorganic salts of the ground substance do not become chemically combined with the collagenous fibrils. The cement substance is supposed to consist of an organic base containing calcium salts.

The uniformity of the arrangement and direction of the fibrillar bundles are characteristic of lamellar bone, and it is typical of lamellar bone that its fibril bundles are arranged concentrically. However, in spongy bone, the arrangement of the lamellae is related grossly to marrow cavities between the trabeculae. It is believed that some of the fibrils of each lamella enter the adjacent lamella and, in this way, bind the lamellae together.

The compacta, or cortex, of tubular bone consists largely of Haversian systems. On the inner and outer surfaces of the compacta, there is usually a system of lamellae running parallel to these surfaces but not related to central blood vessels. These are the *ground lamellae.* The inner ground lamellae are deposited from the endosteum and are present in the diaphysis only when there is no spongy bone—that is, when the marrow is in contact with the compacta.

If the rate of new bone formation exceeds that of resorption, the old Haversian system—that is, the system that is being replaced—splits up, and the fragments of the splintered Haversian system fill the spaces between the Haversian systems, producing the *interstitial lamellae,* which are also called breccie. The Haversian interstitial lamellae form a supporting mass for the Haversian columns of the compacta.

The Haversian systems and fragments of Haversian systems are separated from each other and from the ground lamellae by sharply defined lines known as *cement lines.* They represent the site of resorption of lamellar bone, and on their surface, facing the Haversian canal, new lamellar bone has been deposited. The cement lines divide the bone into innumerable irregular islands of tissue.

Sharpey fibers are present in periosteally formed bone and are derived from the periosteum. They are believed to prevent the displacement of the ground lamellae (supporting function).

(2) *Spongiosa.* Spongy bone makes up most of the mass of the smaller bones, like those of the tarsus and carpus, the bodies of the vertebrae and ribs, and the upper and lower ends of tubular bones.

The *structure* of adult spongy bone can be compared to lattice work. By means of such a structure, considerable strength is attained without undue weight. The strongest laminae run through the structure in those directions in which the bone naturally has to sustain the greatest pressure. The spongy trabeculae and lamellae differ from the Haversian systems in that only the larger trabeculae contain blood vessels, and in comparison with the cortex, the vessels are very few. The fibrillar structure of the trabeculae is no different from that in the lamellar systems. The active cellular bone marrow is supported in the meshes between the spongy bone, and in the diaphysis of long bones of adults, in which the spongy trabeculae are few or entirely absent, the marrow is fatty.

2. Periosteum. Each bone is ensheathed by a relatively tough membrane called the periosteum. In structure the periosteum consists mainly of white fibrous tissue. Beneath this layer is a looser connective tissue which is highly vascular and contains cells capable of becoming active octeoblasts. This layer therefore may be called the osteogenic layer (the *canbium layer*). The function of the periosteum has been subject to controversy. However, it provides a medium for the attachment of muscles, tendons, and ligaments and also has a nutritive function. The controversy over the periosteum concerns the bone-forming properties. If the term "periosteum" is confined to the superficial fibrous layer, it is a limiting membrane. If the term includes the deeper layer, it is osteogenic. It should be remembered that local pressure on the vascular periosteum disturbs the blood supply to the underlying bone, leading to a loss of vitality and subsequent absorption. It is evident, therefore, that hard bone can be extensively molded in the smaller details of its surface features by the soft tissues with which it is in contact. From the deep surface of the periosteum, fine-pointed bundles of fibers run straight into the underlying bone at fairly regular intervals. These are the perforating fibers of Sharpey.

3. Blood Vessel and Nerve Supply. Bone is well supplied with blood vessels which ramify freely in the periosteum. Fine branches from this periosteal network penetrate the underlying bone in small canals (*Volkmann's canals*), and from the latter they are distributed to the system of Haversian canals. The metaphyses are particularly rich in blood vessels; these are derived from the periarticular arterial plexus which is found at the capsular attachment of all joints, and they enter the bone by numerous and often fairly large foramina. These vessels are virtually end arteries with little anastomosis with the main branches. In other words, the epiphyseal plate of cartilage forms a complete barrier between the two vascular territories.

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shaft of a long bone are always directed obliquely away from the growing end of the bone—i. e., in the upper limb toward the elbow and in the lower limb away from the knee. This obliquity is a result of the mode of growth in length of the bone. At the onset, the nutrient artery enters the shaft at right angles and as the shaft extends in length away from the growing end the artery is carried with it, with the result that its entrance becomes more and more oblique in a direction toward the opposite extremity of the bone. Most of the long bones have one nutrient foramen. Some, such as the femur and clavicle, constantly have two.

Fine medulated and nonmedulated nerve fibers enter the bone with the blood vessels and can be followed into the Haversian canal. Of the nerve fibers which reach the bone marrow, most are concerned with the innervation of blood vessels, and it is probable that a few establish a terminal relationship with the marrow cells.

B. OSSIFICATION

1. Factors Initiating Ossification. It is important to recognize that there is a clear distinction between simple calcification and endochondral ossification. The former is a degenerative process related to a poor blood supply and a breaking down of the tissues, whereas the latter is an active growth process accompanied by rich vascularization and tissue proliferation.

The onset of ossification has been supposed by some authorities to be dependent upon mechanical stimuli, particularly by tensile forces and friction. Although observation and eperiment suggest that in certain types of ossification extraneous stimuli provide the conditioning factors, it remains quite certain that the normal appearance of centers of ossification is entirely dependent on intrinsic growth factors. In other words, the development of the elements of the typical vertebrate skeleton has a morphological basis.

Pierre LaCroix has presented experimental evidence which tends to demonstrate that the organization of a skeletal piece and also the osteogenesis produced by the periosteum are under the influence of an organizer; the nature of the organizer is unknown. Experiments have shown that an osteogenic substance can be extracted from the growth cartilage which points strongly toward the existence in the growth cartilage of an organizer. LaCroix believes that osteogenesis is an embryological problem and further experimental work is necessary to clarify the present thought on the subject.

2. Types. There are two commonly described types of ossification of bone: *In membrane (intramembranous ossification) and in cartilage (endochondral ossification)*.

The bones of the appendicular skeleton (with the exception of the clavicle), the trunk, and the base of the skull are cartilage bones. Bones of the skull vault, bones of the face, and the clavicle are membrane bones. The distinction between cartilage and membrane bones is generally assumed to have a morphological basis. This statement has been subjected to controversy. Although the same fundamental processes are involved in intramembranous and endochondral ossification, in certain pathological conditions these two types of bone formation may be independently disturbed. In achondroplasia, the growth of cartilage bones is everywhere retarded,

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leading to deformities. In cleidocranial dysostosis, on the other hand, the ossification of membrane bones is affected.

a. Intramembranous. The onset of ossification is preceded by an increased vascularity of the tissue. Collagenous fibers are collected into bundles in a gelatinous ground substance in which are also congregated numerous branching cells. The latter are osteoblasts. Calcium salts are then deposited in the interstitial substance and on the osteogenic fibers. The bone is laid down at first as fine spicules which interlace to form a spongy texture. Later, with increasing growth, the bone becomes thicker and more dense.

b. Endochondral. The site of commencing ossification is indicated by changes in the cartilage cells. In the middle of the shaft, these become large and vacuolated and tend to arrange themselvces in rows which radiate up and down the shaft from the center. Calcium salts are deposited in an amorphous form in the cartilaginous matrix. This process of calcification apparently leads to the cutting off of nutrient supply to many of the enclosed cartilage cells, and they undergo rapid degeneration and die. Meanwhile, the perichondrium at the middle of the shaft becomes active, and true bone is laid down as a thin shell on the surface by the process of intramembranous ossification. From the deeper layer of the periosteum, an active ingrowth, richly supplied with blood vessels, pushes its way into the center of the shaft, eroding the calcified cartilaginous matrix to do so. The center of the shaft thus becomes vascularized. Osteoblasts and osteoclasts are carried in by this process. The osteoblasts are concerned with deposition of the calcareous basis of bone. They appear to be derived in large part from undifferentiated connective tissue cells.

This invasion by vascular osteogenetic tissue is accompanied by absorption in the area of calcified cartilage, forming large spaces in the center of the shaft. The walls of these spaces are lined by osteoblasts. It is now apparent that calcified cartilage is a temporary scaffolding which is removed bit by bit as it is replaced by true bone.

True endochondral ossification in the center of the shaft proceeds with the deposition of subperiosteal bone on the surface. The extremities of most long bones remain cartilaginous until after birth, when secondary centers of ossification appear in them to form the epiphyses.

3. Nature of Ossification

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by extracellular substances. These changes consist essentially in the creation of a local acidity and the establishment of an available local source of calcium salts. The local source of available calcium is created by the local death of bone and the absorption of calcium by the fibrin of the hematoma. This combination results in supersaturation of the tissue fluid and precipitation of calcium salts in the matrix with the creation of bone.

Factors militating against the humoral theory are: 1. Some connective tissue cells possess greater osteogenic properties than others. 2. There is a

difference in ability of different connective tissues to form bone in the same altered environment.

The low pH in the fracture field is present only while the fibrous callus is forming; hence it would seem that another mechanism is necessary to explain the local holding of calcium during the period of ossification which occurs later. The source of calcium from the damage of local bone would not appear to be of sufficient quantity to be the source of calcium deposited in the periosteal and endosteal callus.

Hastings has formulated the arrangements favorable for bone formation as follows: 1. Optimal physical conditions for the surface precipitation of calcium salts on surfaces which are provided by newly formed fibrils and cement. 2. Optimal chemical conditions which are provided by the existence of calcium ions, phosphate ions, and carbonate ions in the tissue fluid. In order to have precipitation of the double salt $CaCO_3 . 2CA_3(PO_4)_2$, it is necessary that its solubility product constant be exceeded. This might be accomplished by an increase in the calcium, PO_4, of CO_3 ions. Then, by the law of mass action governing difficulty soluble salts, the calcium carbonate and the tricalcium phosphate, which exists as a double salt, will be precipitated together.

b. Role of the Osteoblast. The capacity to form bone depends on the intrinsic properties of periosteal tissue and not on chemical variations in the tissue fluids. Experimental work has shown that, whereas periosteal fibroblasts are apparently incapable of osteogenesis, undamaged osteoblasts formed bone in 100 percent of cases. These findings tend to support the theory that osteoblasts are directly concerned with the deposition of bone. The origin of osteoblastic cells remains in doubt, and the question of the formation of bone from the osteoblasts is not definitely known. However, an enzyme, phosphatase, has been described as a very strong factor in the formation of bone. The enzyme is actually synthesized by osteogenic tissue. Phosphatase has the power of hydrolyzing a soluble calcium-phosphoric ester which is circulating in the blood stream, with the consequent formation of a free salt in the form of calcium phosphate. The latter is then precipitated locally.

c. Role of the Osteoclast. Osteoclasts are probably produced by the fusion of a number of individual cells, and their function is concerned with the absorption of bone.

C. GROWTH OF BONE

1. Growth in Thickness. Growth in thickness occurs as a result of continuous deposition of layers of subperiosteal bone on the surface of the shaft. Coincidentally, the marrow cavity becomes enlarged as the bone grows in size owing to the continuous absorption of the medullary wall of the shaft by the activity of osteoclasts. In the adult bone, therefore, the main part of the shaft must have been derived entirely from the intramembranous ossification of subperiosteal bone, the site of the original bony shaft (ossified in cartilage) having been now replaced by the marrow cavity.

2. Growth in Length. Growth in length results from the gradual extension of endochondral ossification into the cartilaginous extremities. The

latter, as they become encroached upon in this way, grow superficially by the proliferative activity of the cartilage cells and so maintain their integrity. In the first few years after birth, secondary centers of ossification appear in the middle of the cartilaginous extremities to become bony epiphyses which remain separated from the shaft by the epiphyseal cartilage plate. The plates are of importance for continued growth in length of long bones until maturity is reached. This growth is maintained by the extension of ossification from the diaphysis into the diaphyseal surface of the epiphyseal cartilage while the epiphyseal surface of the cartilage continuously proliferates at a corresponding rate. In this way, the epiphyseal cartilage is retained and continues to separate the epiphysis from the diaphysis. When maximal lengths of the bone have been reached, proliferation ceases. The part of the diaphysis immediately adjacent to the epiphysis is sometimes called the metaphysis.

Longitudinal growth of the bones of the endoskeleton through cartilage is less influenced by the removal of mechanical stimuli than is transverse growth through fibrous tissue. This can be seen in such conditions as infantile paralysis or ankylosis from Still's disease with resultant loss of function of the limb; the shafts continue to increase in length and the epiphyses to enlarge at a rate that is only moderately under normal, while at the same time the transverse growth of the shafts may be much retarded or even arrested. The bony centers in the growing epiphyses have over their sides a surface covering of cartilage, the cells of which do not become phagocytic during periods of disuse and are not subject to concentric atrophy.

Although in the large limb bones epiphyses are formed at both ends, growth takes place mainly at one end; in the case of the upper limb, this is at the end farther away from the elbow and in the lower limb, at the end nearer the knee. *The growth of a bone involves not only a continuous accretion on the surface and at the extremities but also a continuous process of remodeling whereby the characteristic shape of the bone is retained.* As the shaft grows in length at the epiphyseal plate, bone at the same time must be removed from the metaphyseal surface by the process of absorption in order to preserve the characteristic contour. However, one process can occur without the other. This is found in a pathological condition, known as diaphyseal aclasis, in which the long bones grow in length at a lormal rate but the remodeling process at the metaphysis is interrupted or irregular (multiple exostoses?). The process of remodeling occurs on the outside and on the cancellous tissue inside.

3. Times of Ossification. In general, the primary centers of ossification of all the larger bones appear at the end of the second month of fetal life. The earliest bone starting to ossify is the clavicle (sixth week). Almost all secondary centers of ossification appear after birth. The dates of their appearance vary considerably from one bone to another and to some extent also in different persons. They are somewhat more precocious in females. The epiphyses at the growing ends of bones are the last to fuse with the diaphyses. In general, also, the epiphyses which join last are the first to commence ossification. An exception to this rule is

found in the lower extremity of the fibula. In the female sex, epiphyses join with the shaft considerably earlier than in the male. (It is also true that the dates of fusion are usually accelerated in normal individuals of short stature and delayed in tall individuals.) The factors which determine the time of ossification are obscure. Size and functional and morphological factors may be involved.

4. Methods of Studying. *One of the earliest facts to be established in regard to bone growth is the absence of all interstitial growth.* In other words, a mass of bone never increases its size by internal expansion but always does so by surface accretion. The use of madder root for the study of bone growth has shown that a long bone grows by accretion, accompanied by the absorption mechanism of remodeling. The diaphysis grows in length at the epiphyseal ends only. The bony epiphyses themselves grow by deposition of bone on their free articular surface. No new bone is added to the diaphyseal side of the epiphysis—some degree of absorption seems to take place here. This example of bone growth emphasizes the great plasticity of bony tissue during development.

The lengthening of the shaft, the appearance and enlargement of the epiphyses, and also, the trabecular pattern of the cancellous tissue can be studied by serial X-ray examination. Bone growth has been found to be influenced by age and sex and also by economic status, the total body weight, and possibly by function. The lines of arrested growth which can occasionally be seen by X-ray in the metaphyses of long bones are local condensations of the trabeculae of cancellous tissue. They can often be related to definite illnesses which have occurred in early life and which have led to a temporary interruption of ossification in the epiphyseal cartilage.

5. Epiphyses.

a. Types. Bony epiphyses are formed from secondary centers of ossification. Those which occur at the articular extremities of the long bones are sometimes termed *pressure epiphyses* and have a protective function. *Traction epiphyses* occur at the site of attachment of tendons and ligaments usually at the ends of the long bones (trochanter). A third type of epiphysis is the *atavistic epiphysis;* they represent skeletal elements which have undergone retrogression and later secondary fusion with bones in the neighborhood.

b. Ossification. Ossification in a cartilaginous epiphysis may commence in one of two ways: *From the vascular tissue in the cartilage canals; or from an invasion of the cartilage by vascular tissue from the perichondrium on the surface.*

6. Metabolic Factors in Bone Growth. The following metabolic factors deserve consideration in bone growth:

a. Calcium Metabolism.

(1) Blood calcium. Calcium is *absorbed* chiefly in the upper portion of the small intestine, the degree of absorption being dependent upon factors which influence the solubility of calcium salts. The most important of these are (1) the hydrogen ion concentration within the intestine and (2) the relative amount of phosphate present. Factors which tend to increase intraintestinal alkalinity will proportionately diminish the degree of absorp-

tion of calcium, and factors which increase intraintestinal acidity will correspondingly increase calcium absorption. If the calcium-phosphate ratio in the upper intestine is high, calcium absorption is diminished, owing to the production of a large quantity of insoluble tertiary calcium phosphate. Disturbances in fat absorption and increased fat excretion act in the same manner because of the presence of large amounts of fatty acids in the intestine. It is believed by some that the chief effect of the antirachitic factor (vitamin D and ultraviolet rays) upon calcium metabolism is to increase calcium absorption from the intestine. It is possible, however, that the main activity of the antirachitic factor may be exerted in the intermediary metabolism of phosphorus and calcium. The details of the intermediary metabolism of calcium are not clearly understood.

Normal adults are in a state of calcium equilibrium. An extremely small amount of calcium in the diet results in a negative calcium balance. A normal calcium equilibrium can be maintained on an adult diet of 1 gm. of calcium for every 100 gm. of protein. Calcium is actively *excreted* into the large intestine, chiefly in the form of calcium phosphate and calcium carbonate.

There is no calcium in the red blood corpuscles; it is contained entirely in the plasma. The calcium content of whole blood varies inversely as the corpuscular volume. The calcium content of human serum normally ranges from 9 to 11 mg. per 100 cc. and is extremely constant under normal conditions.

Serum calcium consists of two distinct fractions: diffusible and nondiffusible. The diffusible fraction is that portion which is capable of passing through artificially prepared membranes and, presumably, through the living capillary wall and cell membrane; the nondiffusible fraction normally cannot, owing probably to its combination with serum proteins. The diffusible portion normally ranges from 4.5 to 5.5 mg. per 100 cc., constituting from 40 to 60 percent of the total serum calcium. It is probable that all the ionized calcium is diffusible and the quantitative relationship between the various calcium states in the blood serum may be expressed as follows:

Total serum Ca=diffusible Ca+nondiffusible Ca
9–11.5 mg.=4.5–5 mg. (ionized)+4.5–6 mg (nonionized)

Factors involved in maintenance of normal serum calcium level and partition are parathyroid hormone, vitamin D, and ultraviolet irradiation, plasma proteins, serum phosphate, and acid-base equilibrium.

The outstanding effect of the administration of active *parthyroid hormone* is an increase in the calcium concentration of the blood serum. It is believed that the physiological action of the parathyroid hormone is to regulate calcium metabolism and maintain a definite level of calcium in the blood. The production of this effect is dependent in part upon the presence of an adequate supply of vitamin D. The knowledge of the mechanism of the action of the parathyroid hormone is limited. Its physiological effects may be outlined as follows: (1) To raise the blood calcium and lower the blood phosphorus; (2) possibly to increase the ionized calcium in the blood; (3) to increase calcium and phosphorus elimination in the urine; (4) to obtain the calcium for this increased demand either from a large amount of in-

gested calcium or from the stores in the bones; (5) to increase the serum phosphatase activity; (6) to decrease corpuscular ester phosphorus. The mechanism that produces these effects is the subject of considerable controversy. However, the primary fundamental effect of the hormone appears to be to increase the diffusible fraction.

Both *vitamin D and ultraviolet irradiation* cause an increase in the concentration of calcium in the blood. Under normal conditions, the effect of vitamin D appears to be dependent upon a normal supply of parathyroid hormone. The effect of vitamin D upon serum calcium, although identical with that of parathyroid hormone, is probably produced in an entirely different manner.

Differences in the modes of action of the two agents (vitamin D and parathyroid hormone) are the following: Vitamin D produces a prompt and relatively marked rise in the inorganic phosphorus of the blood plasma. Parathyroid hormone causes a relatively slight, if any, increase in this element. The picture of osteitis fibrosa cystica has been observed in experimental hyperparathyroidism and is not seen in hypervitaminosis D. Parathyroid hormone does not produce healing of the lesions of rickets; vitamin D does. The serum phosphatase activity is increased in hyperparathyroidism and vitamin D deficiency, the administration of parathyroid hormone causing an increase and of vitamin D in rickets a decrease in serum phosphatase activity. Administration of parathyroid hormone is followed by a decrease in corpuscular ester phosphorus and large doses of vitamin D are followed by an increase.

Because about half of the total serum calcium is bound in some way to the *plasma proteins* (nondiffusible calcium), alterations in the plasma protein concentration may be expected to result in a similar change in the concentration of calcium. The albumin fraction is of greater importance than the globulin fraction.

There is roughly a reciprocal relationship between the concentrations of serum calcium and *serum inorganic phosphate.* This inverse relationship between calcium and phosphorus in the serum is dependent upon many factors, the exact nature of which is not known. The diffusible fraction of serum calcium is the portion affected by changes in the serum phosphate concentration.

The condition of the *acid-base balance* may be an important factor in determining the degree of ionization of serum calcium. It is thought by some that the concentration of calcium ions varies directly with the hydrogen ion concentration.

It is probable that the *cerebrospinal fluid* and *normal tissue fluids* contain the *diffusible fraction of serum calcium.* In the presence of protein in the tissue fluids, the calcium content is increased by an amount proportional to the quantity of protein present, the added calcium being nondiffusible in nature.

Deviation from the normal state of serum calcium may be manifested in two ways: By an alteration in the total serum calcium concentration, and by an alteration in the distribution or partition of calcium in the blood and tissue fluids.

Hypercalcemia occurs in hyperparathyroidism, hypervitaminosis D, nephritis, multiple myeloma, polycythemia vera, increased carbon dioxide tension, and neoplastic disease of bone.

In hyperparathyroidism serum calcium values range from 12 to 22 mg. per 100 cc. This change either may follow the ingestion of parathyroid hormone or may result from the generalized form of osteitis fibrosa cystica. The rise in serum calcium is due to an increase in both the diffusible and nondiffusible forms, although there is a question as to whether or not the primary increase occurs only in the diffusible fraction. The hypercalcemia of hyperparathyroidism is accompanied by the following changes: (1) Primary decrease in serum phosphate, which would be followed later by an increase due probably to renal functional impairment; (2) diminution in corpuscular ester phosphorus; (3) increased serum phosphatase activity; (4) increased urinary calcium and phosphorus elimination; (5) hemoconcentration, with an increase in serum protein concentration; (6) hypochloremia, due probably to an excessive loss of chloride by diuresis.

Hypercalcemia may result from the *administration of excessive quantities of vitamin D.* Clinically, this rarely occurs. *Dihydrotachysterol,* a substance closely related to vitamin D, produces an increase in serum calcium. The effect of the substance appears to be closely analogous to that of parathyroid hormone.

The serum calcium may be increased in rare cases of advanced *nephritis* with uremia. The physiological basis for this mechanism is not clearly understood.

Hypercalcemia occurs in about 50 percent of the cases of *multiple myeloma* and the serum calcium values may range from normal to 20 mg. per 100 cc. The increase in serum calcium may be dependent in some cases upon the increased serum protein concentration which occurs in this condition.

The serum calcium concentration is usually within normal limits in the great majority of cases of primary and *metastatic neoplasms of bone.* In cases of *extensive metastatic involvement,* values may range as high as 22 mg. per 100 cc. In such cases, values for serum phosphorus and serum phosphatase are usually within normal limits. However, in osteogenic sarcoma, the serum phosphatase may be increased.

Hypocalcemia occurs in hypoparathyroidism, vitamin D deficiency, osteomalacia, celiac disease, sprue, nephrosis, and nephritis.

Hypocalcemia is one of the most constant features of *diminished parathyroid function.* As a rule, when the serum calcium falls below 7 mg. per 100 cc. owing to parathyroid deficiency, symptoms of tetany are manifest. The forms of tetany associated with a diminished concentration of serum calcium and possibly dependent upon a state of hypoparathyroidism or vitamin D deficiency are the following:

- Infantile tetany (frequently associated with rickets);
- Tetany associated with osteomalacia (vitamin D deficiency);
- Idiopathic juvenile or adult tetany;
- Tetany following parathyroidectomy.

Deficiency in vitamin D usually causes rickets, and in the great majority of cases the serum calcium is normal, there being a decrease in the level of

serum phosphate. In some instances, however, hypocalcemia occurs, with manifestations of tetany.

In osteomalacia the serum calcium level may range from 5 to 7.5 mg. per 100 cc., with associated manifestations of tetany. Osteomalacia apparently resembles the low calcium form of rickets.

In celiac disease there is defective absorption of fat from the intestine, resulting in the formation of large quantities of insoluble calcium soaps; hence the absorption of calcium is inadequate, as is also vitamin D. Delayed ossification and osteoporosis occur commonly.

In nephrosis the diminution of serum calcium is due entirely to a decrease in the nondiffusible fraction which occurs as a result of a marked diminution in the concentration of serum protein.

Alterations in distribution of calcium are manifested during the course of pregnancy and in alkalosis. During the course of *normal pregnancy* and early labor there is a gradual diminution in the level of total serum calcium. The level, however, rarely falls below the limit of normal.

In alkalosis there is a diminution in the proportion of ionized calcium which is responsible for the symptom complex, tetany. Usually the serum calcium in these conditions is within normal limits and the decreased ionized partition is the responsible culprit. This condition occurs clinically (*a*) Following the administration of excessive quantities of alkali; (*b*) as hyperventilation; (*c*) in association with pyloric and acute upper intestinal obstruction or excessive vomiting (gastric tetany), the level of serum calcium being normal in each instance.

(2) *Urinary calcium. Under normal conditions,* 10 to 30 percent is excreted in the urine.

Urinary calcium is increased in hyperparathyroidism, hyperthyroidism, acidosis, and hypervitaminosis D.

In hyperparathyroidism 70 to 90 percent of the calcium is eliminated in the urine and only 10 to 30 percent in the feces.

In hyperthyroidism the urinary calcium is increased to about 56 percent; the decrease is due to a direct stimulating effect of calcium deposits in the bone.

There is an increased total excretion of calcium in *acidosis,* and this increased excretion is due almost entirely to an increase in urinary calcium, which in all probability has been abstracted from the bones.

Hypervitaminosis D has effects on calcium excretion similar to those of hyperparathyroidism.

Urinary calcium is decreased in hypoparathyroidism, hypothyroidism, ingestion of bases, chronic nephritis, and calcinosis universalis.

(3) *Fecal calcium. Normal:* Under normal conditions 70 to 90 percent of the calcium is excreted in the feces.

An increase in the quantity of calcium eliminated in the feces may be observed in rickets and osteomalacia (vitamin D deficiency), in sprue, and in celiac disease. In sprue and celiac disease the increase is due to defective calcium absorption, resulting in the formation of insoluble calcium soaps in the intestine. In rickets and osteomalacia it is thought that the fundamental defect is in the intermediary metabolism of calcium and phos-

phorus, whereby normal ossification cannot occur and an increased quantity of calcium is eliminated into the lower bowel.

b. Phosphorus Metabolism.

(1) Blood Phorphorus. The *absorption of phosphates* from the intestine is governed by the same factors as those which influence the absorption of calcium. Therefore, a marked diminution in the alkaline reaction in the upper intestine favors phosphate absorption; the presence of a relatively large proportion of calcium or magnesium tends to inhibit phosphate absorption, perhaps by the formation of insoluble, tertiary calcium phosphate. The absorption of phosphate from the bowel is also dependent upon the utilization of calcium in the body. Some is undoubtedly absorbed in the upper intestine. A large amount of phosphate is *secreted* into this portion of the bowel and is reabsorbed in the lower intestine, the amount of resorption being inversely proportional to the excretion of calcium into the lower bowel. If there is a decreased utilization of calcium in the tissues, this element is *excreted* in relatively large quantity and the absorption of phosphate is correspondingly diminished.

The normal inorganic phosphate blood serum value ranges from 3 to 4.5 mg. per 100 cc. in adults and from 4 to 6 mg. per 100 cc. in children. Under normal conditions the blood phosphate level varies directly with the concentration of ultraviolet rays, being highest in summer and falling during the winter. Variations in the phosphate content of the serum occur normally during periods of varying carbohydrate utilization owing to the fact that combinations of carbohydrate and phosphoric acid play a role in the intermediary metabolism or carbohydrate.

(c) Abnormalities. Hyperphosphatemia occurs in hypervitaminosis D, hypoparathyroidism, and renal failure. An increase in serum phosphorus concentration sometimes occurs in acute high intestinal obstruction.

The serum phosphate concentration may be increased by therapeutic or *excessive doses of vitamin D.*

Decreased parathyroid function is associated with a slight rise in the serum phosphate concentration which is more or less proportional to the diminution in serum calcium.

Increase in the concentration of serum phosphate in patients with *chronic glomerulonephritis* is an indication of renal functional insufficiency. Values as high as 40 mg. per 100 cc. have been reported. Similar alterations in the serum phosphate concentration may occur in—

Renal insufficiency associated with nephrosclerosis;
Multiple myeloma,
Destructive kidney lesions, such as congenital polycystic kidney, tuberculosis, malignancy, pyonephrosis, pyelonephritis, and hydronephrosis.

Hypophosphatemia occurs in rickets, osteomolacia, hyperparathyroidism, idiopathic steatorrhea, and increased carbohydrate utilization.

In rachitic children, serum phosphate values from 1 to 2 mg. per 100 cc. are commonly observed. This condition is believed to be due fundamentally to vitamin D deficiency, which operates either by diminishing the degree of absorption of phosphorus and calcium or by preventing their proper utilization in the process of ossification. In some cases of rickets the serum

phosphate concentration may be within normal limits, the serum calcium being diminished (low calcium rickets). In such circumstances the rachitic condition is commonly complicated by infantile tetany. If the concentration of calcium is multiplied by that of phosphate, a product is obtained which, in the normal child, ranges from 50 to 60. When the product is below 30, rickets is present; when it is above 40 either healing is occurring or rickets has not been present.

Diminution in the concentration of serum phosphate is one of the most constant features of *osteomalacia.* The metabolic disturbance in this condition is believed to be similar to that in rickets, both being probably dependent upon vitamin D deficiency.

The *injection of parathyroid hormone* is followed by a diminution in the concentration of serum phosphate, which is perhaps a result of the increased elimination of phosphate in the urine. The decrease in serum phosphate is roughly proportional to the increase of serum calcium in this condition. Repeated administration of parathyroid hormone or prolonged primary hyperparathyroidism is associated with a decreased elimination of phosphate in the urine and an increase in the serum phosphate. This effect is due to the development of renal functional insufficiency, and at the same time one notices an increase in the nonprotein nitrogen.

The characteristic fatty diarrhea in *idiopathic steatorrhea* is frequently accompanied by skeletal demineralization, dwarfism, low serum calcium and phosphorus, and at times characteristic manifestations of rickets and tetany. The abnormalities of calcium and phosphorus metabolism are secondary to the large quantity of fat in the bowel and are due to the defective absorption of calcium, phosphorus, and vitamin D.

(2) *Urinary phosphate.* Under *normal* conditions about 30 percent of the injested phosphate is eliminated in the feces and 70 percent in the urine. One of the important means by which the kidney aids in maintaining the acid-base balance resides in its ability to transform the basic phosphate B_2HPO_4 of the blood to the acid phosphate BH_2PO_4 which is eliminated in the urine. In the presence of *acidosis* or *factors which tend to produce acidosis,* the elimination of acid phosphate in the urine is greatly *increased.*

The *administration of parathyroid hormone* results in an *increase* in the quantity of phosphate eliminated in the urine. An increase in urinary phosphate has also been observed in clinical hyperparathyroidism. In *hypoparathyroidism,* the urinary phosphate is *diminished.* Urinary phosphate is diminished in rickets, the greater part of the phosphate being excreted in the feces. The administration of vitamin D or ultraviolet rays increases the urinary elimination of phosphate in rickets and osteomalacia.

c. Phosphatase.

(1) *Alkaline.* Phosphatase is an enzyme capable of hydrolyzing practically every monophosphoric ester, both aliphatic and aromatic, including a portion of the phosphoric esters of the circulating red blood cells and those present, in small amounts, in blood plasma. In the fetus and growing animal, the greatest relative quantity of phosphatase is found in the bones and teeth. In the adult animal, the intestinal mucosa contains the greatest amount per unit of weight. The identity of the phosphatases of bone, in-

testinal mucosa, kidney and blood plasma has been fairly definitely established on the basis of the similarity of certain factors. However, the phosphatase enzyme present in red blood cells is different from that in other tissues.

According to the method of Bodansky, a unit of phosphatase activity is defined as "equivalent to the actual or calculated liberation of 1 mg. of phosphorus as the phosphate ion during the first hour of incubation at 37° C. and pH 8.6, with the substrate containing sodium betaglycerophosphate, hydrolysis not exceeding 10 percent of the substrate." The *normal value* for adults is 1.5 to 4.0 Bodansky units per 100 cc. and for children 5 to 14 units per 100 cc.

The hypothesis of Robison and Soames regarding the mechanism of normal calcification of bone is important and may be stated as follows: The osteoblasts, the hypertrophic cartilage cells, and certain cells of the inner portion of the periosteum in a growing bone contain, or can secrete, a very active phosphatase which, by hydrolyzing the salts of phosphoric esters brought to the ossifying zone by the blood stream, causes a local increase in the concentration of phosphate ions. The solubility product for calcium phosphate, which is probably very nearly reached at the concentration of inorganic phosphate and ionized calcium normally present in the circulating blood plasma at normal plasma pH, is thus exceeded locally, and a deposition of the calcium phosphate is brought about in, or in the neighborhood of, the cells which secrete the active enzyme. This mechanism is important in the theory of calcification of bone; however, such factors as (1) serum calcium and phosphate concentration, (2) the parathyroid hormone, (3) thyroxin, (4) vitamin D, (5) calcium and phosphorus intake and absorption from the bowel, and (6) the state of the acid-base balance must be considered.

The serum phosphatase activity is consistently *increased in active rickets.* Values over 60 units may be observed in severe rickets. With the institution of antirachitic therapy the serum phosphatase activity decreases, usually after an interval of 4 to 12 days. A high normal figure may be reached within 2 months and is frequently maintained for some time during the period of active repair. When bone reconstruction is complete, the serum phosphatase is within normal limits. It has been shown that the plasma phosphatase activity may remain above normal even after healing is apparently complete by X-ray examination. Many observers believe that the determination of plasma phosphatase activity may be regarded as a reliable means of detecting latent and active rickets and may be accepted as an index of improvement in this condition.

A moderate *increase* in serum phosphatase activity occurs in *hyperparathyroidism* and values as high as 65 units have been reported, the average range being 20 to 40.

Increased serum phosphatase activity has been observed rather consistently in Paget's disease involving several bones. Values to 125 units have been observed in the polyostotic variety and values to 23 units when the disease is localized in one to two bones. Age appears to be a factor, the oldest patients showing the lowest values. The finding of increased alkaline

phosphatase activity together with normal values for serum calcium and phosphorus is of diagnostic significance in this condition.

Miscellaneous Bone Disorders. Elevated values for serum phosphatase activity have been reported occasionally in such conditions as (1) generalized osteoporosis, (2) marked hyperthyroidism, (3) osteomalacia, (4) metastatic carcinoma involving bone, (5) osteogenic sarcoma, (6) gaucher's disease with bone resorption, and (7) marble bones. An occasional elevation may occur also in multiple myeloma.

(2) *Acid.* In 1936, Gutman, Sproul, and Gutman showed that prostatic cancer contains large amounts of acid phosphatase. Normal King and Armstrong values are, for acid phosphatase, less than 4.5 units and, for alkaline phosphatase, less than 12.5 units, each per 100 cc. of serum; in Bodansky units, values range from 0 to 1, and values from 1 to 3 are not co[illegible]

ph[illegible]

of serum are significantly elevated only in cancer of the prostate and in this condition only when metastasis has occurred. When the serum acid phosphatase is significantly raised (and then greater than 10 units by the King and Armstrong method) it is certain that the patient has prostatic cancer with metastasis; values between 5 and 10 units are presumptive of prostatic cancer but are occasionally observed in other conditions. Patients frequently have advanced prostatic cancer, even with metastasis to the bones, accompanies with serum phosphatases in the normal range; but if both phosphatases are distinctly increased, the diagnosis is established that cancer of the prostate with osteosclerotic osseous metastasis is present.

d. Vitamins. *For vitamins A and C,* see section on physiology of vitamins. For *vitamin D,* see section on calcium and phosphorus metabolism and section on physiology of vitamins.

e. Endocrines. The pituitary, thyroid, gonads, and the parathyroids are the glands of internal secretion which are known to influence skeletal growth either directly or indirectly.

The *secretion of the anterior lobe of the pituitary augments bone growth. Hyperfunction* in man causes gigantism and delayed closure of epiphyseal lines if it begins before normal growth is complete and acromegaly if it begins afterwards. *Hypofunction* in young animals causes dwarfism, the retardation of growth of the bones and testis being more marked than that of the other tissues. Feeding such animals anterior lobe extract causes them to grow, indicating that the growth-stimulating hormone is formed there. It is assumed that the eosinophilic cell secretes the growth-promoting principle because pituitary gigantism and acromegaly are nearly always produced by an eosinophilic adenoma.

The effect of the *gonads* on bone growth is less well-known. Castration and congenital or acquired *hypofunction* of gonads delay the time of closure of the epiphyseal lines sometimes for a great many years, which establishes the possibility of longitudinal growth beyond the usual span. In some cases such growth seems to continue and mild degrees of gigantism may rarely result. In the great majority of cases there appears to be no further [illegible] ıeight does not exceed that of the average adult.

Hypofunction of the *thyroid* gland as seen in cretins results in dwarfism during the normal period of bone growth and in persistence of the open epiphyseal lines, sometimes to well past middle life. Slight longitudinal growth may continue during adult life, but it never makes up the deficiency.

Some believe that the thyroid secretion probably affects bone growth only indirectly by its action on the anterior lobe of the hypophysis. Thyroid subnormality depresses pituitary function—i. e., production of the thyrotropic pituitary hormone—resulting in cretinic drawfism.

Bone growth during *hyperfunction* of the thyroid (thyrotoxicosis) has not been studied in children, except for relatively short periods and almost entirely after the tenth year. Aub and coworkers have observed osteoporosis with increased excretion of calcium and probably of phosphorus in adults, but there is little evidence that permanent underdevelopment of the skeleton results from juvenile thyrotoxicosis. The effect of prolonged overfeeding of thyroid to young animals has not been accurately determined.

Chronic parathyroid deficiency following goiter operations with removal of parathyroid tissue has not been reported in children, but in adults it has not resulted in changes in the bones. A continued *excess of parathormone* in the blood, whether from injection in animals or from parathyroid tumor, results in withdrawal of calcium salts from the bones and hypercalcemia. In the seven reported cases of parathyroid tumors with hyperparathyroidism in children there has been little said about bone growth but osteoporosis has been a constant finding, cysts and "giant cell tumors" being absent. Despite the presence of osteoporosis, enchondral bone growth continues in the epiphyses and at the ends of the shafts; yet transverse growth of shaft by fibrous ossification is practically suspended. (See subparagraph e above on physiology of endocrines.)

7. Role of the Sympathetic Nerves. The sympathetic nerves appear to play no special role in bone growth. Cannon and coworkers observed unaltered growth after total excision of the sympathetic chain on either one or both sides in young cats. Bisgard observed no difference in the hind limbs of growing goats after unilateral excision of the lumbar ganglia and no acceleration of growth from the same procedure carried out on the paralyzed side of a monkey with experimental poliomyelitis. On the other hand, Harris reported increased longitudinal growth after lumbar sympathectomy in cases of retarded growth in one leg from poliomyelitis. Muscle regeneration might play a role in such cases.

8. Effect of Infectious Diseases. Growth retardation with delayed puberty may occur in case of prolonged infectious disease during childhood and adolescence. It is seen especially in severe tuberculosis of the spine or hip. It is problematical as to how the infection delays growth, but it may be by depressing the hypophysis, which secondarily affects the bones and testicles.

D. MECHANICS OF BONE

Bone in its internal structure is adapted to resist the stresses and strains to which it is subjected during life and is required to have strength of two kinds: (1) to resist compression or crushing forces and (2) to resist tensile or disrupting forces. The tubular character of long bones is readily ex-

plained on mechanical principles. It is the best construction for resisting bending forces in any direction. In the skeleton, the tubular character of the long bones also makes for lightness and economy of material. The bony lamellae of cancellous tissue can be divided into two types: (1) Pressure lamellae, which develop in response to compression forces and (2) tension lamellae, which are related to tensile forces. The fact that there is conformation of lamellar patterns in cancellous tissue to lines of stress and strain is sometimes referred to as Wolff's law. These lamellae are developed in direct response to mechanical stimuli, though the precise nature of this response is not understood.

1. Influence of Mechanical Factors on Shape of Bone. The account just given has emphasized the power of self-differentiation in bone development. However, it does not account for the finer details and markings which are formed on a normal bone. There is no doubt, that in the later developmental stages, the refinements and details of bone contour are conditioned to a large extent by extrinsic factors and depend upon normal functional activity. The less conspicuous ridges and depressions on the surface of the bone owe their origin to the tension of muscles and ligaments and to the pressure of adjacent structures. The shape of a mature bone can be quite markedly disturbed by abnormal activity, and many examples of this fact can be set forth (dislocated hip) to emphasize the plasticity of bone and its ability to respond to the mechanical requirements of new functions which are imposed upon it. However, it seems that postural adaptations are the result of an alteration in normal growth, probably due to the changed distribution of pressure on the epiphyseal plates of cartilage at the growing ends of the bones.

2. Relation of Function to Structure of Bone (Wolff's Law). On the basis of the appearance of spongy bone in the upper end of the femur, there has been developed the theory of the transformation of bone due to mechanical influences exerted on it. The inner architecture of the spongy bone in this region is supposed to be conditioned by external stresses and strains exerted upon the bone. There is much difference of opinion as to the proper interpretation of the inner structure of the femur.

Origin of the conception of Wolff's law. Those who believe that bone is transformed by mechanical influences exerted on it base their beliefs on the observations that the mechanical structure of the normal femur conforms closely to the mathematical proportions of a structure of similar shape and physical properties, the Fairbairn crane. After mathematical analysis, the conclusion was reached that the cancelli lie along the paths of maximum internal stress and thus transmit a maximum load in the bone with a minimum of material.

The Law. The normal external form and internal architecture of the human femur result from an adaptation of form to the normal mechanical demands on, or normal function, of this bone.

Objections to the Law. Objections are brought forth by those who believe that phylogenetic and hereditary factors are important, if not most important.

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the metaphysis of the bone, osteogenesis begins from the endosteum of the entire surface of injured cancellous bone as early as the third or fourth day. In fractures of the shaft, new bone is found subperiosteally between 5 and 10 days, usually earlier than this in very young persons and later in the aged.

The new bone calcifies completely, incompletely, or not at all as it is laid down in different parts of the callus, but, in general, there is considerable delay in calcification, with the result that osteoid tissue is abundant in histological sections of fractures in young persons and adults on modern diet. After the callus reaches its maximum size, the existing osteoid is rapidly clacified, and nearly all further new bone formation occurs simultaneously with calcification. Osteoid borders are almost always demonstrable in the callus, but this observation may not be interpreted that a stage of osteoid is necessary for osteogenesis or callus formation. The routine clinical roentgenogram of the fracture site does not show the new bone for some time after it is deposited or until it increases in density, and throughout healing, regardless of the state of calcification, the newly deposited spongiosa outlining the callus is not much denser than the large muscles around it.

Chondrogenesis takes place mainly between the fracture ends and results in the formation of a disk of fibrocartilaginous callus consisting of dense fibrous connective tissue, fibrocartilage, and hyaline cartilage. The disk of fibrocartilaginous callus extends outside the fracture ends, separates the deposits of new bone on the fragments on either side of the fracture line, and occupies the clear space of the fracture gap when viewed in the roentgenogram. In addition to the main mass, small islands of hyaline cartilage may be seen histologically almost anywhere in the mass of the bony callus.

Ossification of the dense fibrous connective tissue of the callus is accomplished by simple intramembranous bone formation. The fibrocartilage and hyaline cartilage are replaced by bone in a variety of ways:

a. Bone is laid down on calcified matrix of previously invaded cartilage forming primary spongiosa.

b. Resorption of cartilage and deposition of bone occur simultaneously.

c. Immature hyaline cartilage and fibrocartilage are included and calcified in bone trabeculae, resorption being delayed.

d. Apparent transformation of chondrocytes into osteocytes is seen with the structure of the bone trabeculae.

Cartilage matrix calcifies superficially wherever it comes into contact with osteogenic tissue. Only the intercellular substance of bone and cartilage in the callus is capable of calcification, for, except for rare instances of calcified, hyalinized dead fragments of soft parts undergoing absorption, all other tissue, including the original hematoma, is replaced by bone without preliminary or intermediate deposition of calcium salt.

A large part of the shaft enclosed in callus is resorbed by the formation of osteoclasts, osteoblasts, and spindle-shaped cells which are byproducts of the bone. Bone salt is transferred from the shaft to the callus in this process, but this source is slowly developed and submits only a very small contribution to the total calcium deposited in the fracture callus at any one time.

The new bone calcifies almost entirely through the deposition of calcium and phosphate ions and, presumably also, primary calcium phosphate trans-

3. Self-Differentiation of Bone. The development of the main anatomical features of a bone depends upon intrinsic growth factors, and this development is independent of the influence of extrinsic mechanical or chemical stimuli; the potentiality resides in the tissue itself. The bony articular surfaces of joints can similarly be formed by intrinsic differentiation, with no relation to the attachment of muscles or to the initiation of movements in the fetus.

E. FRACTURE HEALING

1. Immediate. The immediate effect of a fracture is rupture of the continuity of the osseous tissue with extravasation of blood which does not clot entirely for from several hours to the end of the first day. If the fragments are displaced, as necessarily occurs in the initial injury when the fracture is complete, it is common to find contusion and laceration of muscle, displacement of fragments of bone, bone marrow, muscle, and fascia, and, rarely, compression of tendon and nerve between the cortical ends. In fractures through the ends of the bones, pieces of articular cartilage and capsular ligament may be dislodged and displaced into the fracture gap and included in the hemorrhagic tissue.

2. At Time of Orthopedic Treatment. The handling of a fractured limb in the course of clinical treatment and the manipulations necessary for reduction produce further motion and friction at the injured surfaces of the bone and additional hemorrhage, dislodgment, and displacement of fragments of the various tissues at the fracture site. However, such evidence of secondary injury produced by treatment is mainly histological in uncomplicated cases.

3. In From One to Forty-Eight Hours. Aseptic inflammation occurs in all the injured tissues at the fracture site. Organization begins in the interstitial blood clots in the injured bone and soft parts and on the surface of the hemorrhagic mass in the fracture gap.

4. In From Two to Thirty Days. The hemorrhagic mass is encapsulated in granulation tissue which becomes fibrous connective tissue; as layer on layer of the blood clot become organized and replaced by granulation tissue, the outer parts, developing into fibrous connective tissue, also show differentiation of fibrocartilage and hyaline cartilage. The fragments of dead soft tissue and bone, including the necrotic cortical ends, are absorbed in various ways characteristic of the different histological structures of each tissue. A certain amount of interposed soft tissue is common in fractures of the large long bones and usually is absorbed without interfering with the essential processes of bone regeneration.

5. From Four Days to the Time of Union. Intramembranous new bone formation arises between the periosteum and the shaft and upon the cancellous bone lining the marrow cavity, forming collars of bone on the medullary and periosteal surfaces of each fragment for some distance from the fracture line. The new bone originates in the proliferation of spindle-shaped cells in the inner periosteum and in the endosteum, which resemble fibroblasts but which are termed "resting osteoblasts" because they exhibit increasing basophilia and growing prominence of the nuclear Golgi net as they differentiate into true osteoblasts and bone cells. In fractures through

7. After the Fracture Is United. The external and intramedullary bony callus is resorbed gradually as the bone laid down between the cortical ends reaches the density of the original shaft. After several months to a year, the defect in the original bone is often so flawlessly repaired that the site of the fracture cannot be found.

F. FATE OF BONE GRAFT

The behavior of the fully matured bony elements, whether they are derived from cancellous or from compact bone, presents no great difference. The mature bony elements once transplanted do not, for the most part, survive. They constitute a mass which is so inert that it does not provoke even a foreign body reaction and sooner or later will be replaced by that process known as creeping substitution. This process is exceedingly slow and extends over many months, with a gradually subsiding impetus. In any graft, whether of cancellous or of cortical origin, the only elements which survive and which possess osteogenetic power in any degree are the cells which form the so-called endosteal layer. This is also true, but to a lesser extent, of the elements of the cambium layer of the periosteum. Once these two fundamental features are appreciated, the relative merits of cancellous over cortical bone grafts become immediately apparent.

1. Cortical Bone. In the case of the cortical bone, the greater bulk of the graft is made up entirely of fully mature osseous elements. The endosteal layer is often absent or, when present, is excedingly limited in amount. As for the most part the mature elements fail to survive, the graft itself exists, therefore, as an inert body which can serve only for a limited length of time as an internal splint. Before such a graft can be wholly replaced by living bone, its mass must be entirely removed. This can occur only by revascularization, leaching out of the mineral elements, and autolysis of the collagenous scaffolding. The very physical nature of cortical bone prohibits rapid substitution. The only pathways which a cortical graft presents for the ingress of new blood vessels are the small Haversian canals and the immediate surfaces in contact with the graft bed. Furthermore, since after the trauma of operation, the formation of new vessels reaches its critical point within a few days and thereafter, with changes in biochemical conditions, starts to decline, the progress of penetration is choked off, and many regions of the graft remote from the vascular bed may never obtain a vascular supply. The cellular elements of the capillary tufts possess, as is well-known, considerable potentiality in the direction of osteogenesis; but for osteogenesis to occur, an accommodation space must be available. Such space is not available in the case of cortical bone until the original collagenous elements have been removed to provide for it. The graft, therefore, is in a sense, a deterrent to the formation of new bone. New bone is laid down only on the surfaces of the graft, and, therefore, cortical grafts are frequently found becoming incorporated in, rather than replacing, new bone.

2. Cancellous Bone. The mature elements of the cancellous trabeculae behave in much the same manner as that described for cortical bone, but each and every one of these trabeculae is provided with an endosteal surface

ported by the blood plasma and the intercellular fluids. The delay in calcification of the new bone deposited in the early stages of healing may be explained by the observations that the rate of osteogenesis is greater than the rate at which the calcification mechanism operates with the level of the serum calcium and the particularly low level of the serum phosphorus found in persons other than infants and very young children. Calcium salt mobilized from necrotic or transplanted bone does not diffuse interstitially in a form prepared for redeposition in new bone and is carried out into the general circulation.

The levels of activity of blood calcium, phosphorus, and alkaline phosphatase are not elevated significantly during fracture healing.

The injured soft parts about the fracture site become scarified rapidly, but they show a prolonged inflammatory reaction throughout healing and after the fracture is united. The outer periosteum, the perimysium, and muscle, compressed by the expanding callus, exhibit perivascular round-cell infiltration and formations of lymphoid tissue and lymphoid nodules.

These various processes continue simultaneously in different parts of the callus in a pattern of extremely irregular appearance, but they are so organized that successively granulation tissue replaces hematoma; fibrous connective tissue, fibrocartilage, and cartilage supplant granulation tissue; and bone from either fragment grows into the whole mass of fibrocartilaginous callus between the fracture ends. Union occurs when the growth of bone projected from one fragment meets that from the other and is reorganized between the cortical ends so as to repair the shaft.

The chronological sequence of the foregoing events is approximately the same in fractures of any normal bone. The exact time of their appearance including the development of union varies considerably with (1) individual bones, (2) age of the patient, (3) type of fracture, (4) site of the fracture—metaphyseal or diaphyseal, (5) amount of displacement of the fracture ends, (6) volume of interposed fragments of injured tissue, and (7) general constitutional conditions—nutritional and subclinical pathological states.

The blood supply of the callus consists of new vessels derived from the subperiosteal and metaphyseal perforating arteries and the nutrient artery, which develop temporarily and acquire size and complexity corresponding to the volume of the bony callus.

6. At the Time Union Is Developed. Fractures through the spongiosa of the metaphysis show direct extension of bone growth behind parallel osteogenic fronts advancing from the injured surfaces of the fragments.

In fractures of the shaft of a large long bone and at all sites where nonunion is common, a special course of growth is observed. In cross section, this has been shown to follow the mechanical requirements of the design and dynamics of a fixed-arch bridge. Before compact bone is deposited between the fragments, an arch of external bony callus is developed over the fracture gap. The fracture is united when new cortical bone is formed by growth extending centripetally from the external callus to the bone ends in the same way that the deck of a bridge is laid from the arch.

II. JOINTS

A. MORPHOGENESIS

In a human embryo, the anlage of most joints is complete at the beginning of the third fetal month.

The articular disk of mesenchymal tissue which is primarily formed between the extremities of cartilaginous skeletal elements undergoes absorption in diarthrodial joints, apparently as the result of the pressure of the growing cartilages. This growth leads to a compression of the disk centrally and to the appearance of a cavity in its circumferential portion. The cavity expands gradually and extends towards the center of the joint. The formation of a definitive joint cavity has not been observed in an explanted limb bud; this fact suggests that movement may be a factor in determining its appearance.

Although the actual formation of a joint may depend on extrinsic factors or else on intrinsic factors which are not rigidly localized, the precise shape of the articular surface is certainly determined by definitely localized morphogenetic factors. Tissue culture experiments demonstrate that the initial stages in the development of a joint can occur in the absence of all movement.

B. CLASSIFICATION

For convenience of description, some classification of joints is desirable. There are several ways of doing this, but, on the whole, a broad functional division is most practicable. Thus, one may recognize immovable joints, or *synarthroses;* freely movable joints, or *diarthroses;* and, as an intermediate category, *amphiarthroses,* or partially movable joints. All diarthroses are formed by cartilage-covered articular surfaces, separated by a joint cavity, which is lined by synovial membrane. In synarthroses and amphiarthroses, on the other hand, the articulating bones are united directly by fibrous tissue or cartilage.

1. Synarthroses. Besides the fact that they are not formed for the purpose of movement, these joints have certain other features in common. They represent a persistence of the embryonic stage of development in which the articulating elements are united by a solid articular disk. Where these are cartilage bones, they become joined by a plate of hyaline cartilage; where they are membrane bones, the union is affected by fibrous tissue.

a. Synchondroses. Immovable joints which are of an entirely temporary nature become obliterated as soon as the growth of the articulating bony elements is complete. An obvious example of this type of joint is the union between the diaphysis and epiphysis of a long bone by the

possessing great osteogenetic power. In addition, there are the numerous marrow spaces. The bone marrow cells themselves undergo rapid degeneration and provide wide channels for the invasion of new vessels and eventually for the accommodation of newly formed bone. The cells of the endosteum rapidly come into relationship with a vascular bed, which accounts not only for their survival but for the early proliferation and establishment of new bone. New trabeculae and the incorporation of the old are the characteristic picture in cancellous grafts. The old elements, being small, and lying in such close relationship to vital elements, are removed and replaced more rapidly, although they, too, may remain for many months before complete substitution. It should be pointed out that there is some difference between cancellous bone in which the marrow is highly fatty and that in which red marrow predominates. Fat has, as is well known, an inhibitory effect on the formation of new vascular tufts, and where it is present to excess the process of bone formation is retarded. This would account for the superiority of iliac bone, or bone obtained from other sources containing red marrow, over the fatty cancellous bone found, for example, in the lower end of the femur or the upper end of the tibia.

These distinctions are best seen in the case of grafts derived from ribs where both elements—compact and cancellous bone—are present. The compact tissue of the rib differs slightly from that obtained from other sources in that its Haversian spaces are more numerous and larger, thus allowing a more ready access to new vessels. The cancellous element is like that of other bones. In such grafts one notes a rapid formation of new osteogenic tissue about the trabeculated elements, in comparison to the slow and restricted process of creeping substitution occurring in the cortical portion.

II. JOINTS

A. MORPHOGENESIS

In a human embryo, the anlage of most joints is complete at the beginning of the third fetal month.

The articular disk of mesenchymal tissue which is primarily formed between the extremities of cartilaginous skeletal elements undergoes absorption in diarthrodial joints, apparently as the result of the pressure of the growing cartilages. This growth leads to a compression of the disk centrally and to the appearance of a cavity in its circumferential portion. The cavity expands gradually and extends towards the center of the joint. The formation of a definitive joint cavity has not been observed in an explanted limb bud; this fact suggests that movement may be a factor in determining its appearance.

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epiphyseal cartilage. Synchondroses are also found in the base of the skull between the basioccipital and basisphenoid bones and between the exoccupital and the petrous portion of the temporal bone.

b. Sutures. In these articulations, denticulated bony edges are firmly interlocked and joined together by fibrous tissue.

There is experimental evidence to suggest that the position of sutural lines is morphologically predetermined before the process of ossification is complete, though there may be individual variations in the details of the suture pattern in the adult skull. Corresponding sutures may show considerable differences in their complexity, and there may be scattered along them little separate ossicles (*wormian bones*) which are formed by the detachment of ossifying spicules at the margins of the growing bones.

Closure of sutures. The membrane bones of the skull expand in their growth mainly by deposition of new bone on their outer surface and absorption from their deep surface. Sutural lines do not, therefore, represent the only zones of growth of these bones. Nevertheless, there is a broad relation between suture closure and the growth of the skull as a whole.

Normally, the cranial sutures start to become obliterated at about the age of 30. This process occurs first where the sutures are simplest, and the complex sutures are the last to disappear. It follows from this fact that synostosis first becomes evident on the endocranial aspect of the skull. Suture closure occurs somewhat earlier in the male sex.

c. Gomphosis and Schindylesis. Besides synchondroses and sutures, two other types of synarthrodial joints have been defined. These are the gomphosis, in which the joint consists of a peg fitting into a socket (e. g. the articulation of the teeth with the jaws), and the schindylesis, in which a bony plate fits in a groove (e. g. the articulation between the vomer and the bony palate).

2. Amphiarthroses. These joints differ radically from synarthroses in the facts that they have no relation to the growth of the articulating bones *and are, therefore, completely permanent and that they permit some* degree of movement. Two types are recognized, *syndesmoses* and *symphyses,* depending on the nature of the tissue which unites the articulating surfaces

a. Syndesmoses. In these joints, the opposed bony surfaces are bound together simply by fibrous tissue. It is doubtful whether they should be included in a separate category, for the fibrous tissue is merely a well-developed interosseous ligament, such as is commonly found in diarthrodial joints where movement is slight

b. Symphyses The essential anatomical features of a symphysial joint are that (*1*) *The articulating bony surfaces are covered by a layer of hyaline cartilage and that* (*2*) *these cartilaginous surfaces are united by fibrous tissue or fibrocartilage.* The latter may form relatively thick disks, which, by virtue of their elasticity, allow a fair amount of play between the articulating bones. This is the case, for example, with the joints between the bodies of the vertebrae which are separated by intervertebral disks. This is partly explained by the fact that in the center of each disk is a mass of semifluid pulpy material (the nucleus pulposus), which, incidentally, is

believed to be derived from the remnants of the notochord of the embryo. This central core not only augments the torsional elasticity of each disk as a whole but, functioning in the manner of a water cushion, it also adds to its resilience as a buffer, minimizing the effects of intermittent stresses transmitted along the length of the vertebral column.

The interpubic joint is another example of a symphysis. One interesting feature of this joint is that it usually contains a rudimentary cavity in the form of a vertical slitlike cleft in the middle of the fibrocartilaginous plate. It has been observed that this cavity becomes enlarged in women at the end of pregnancy, leading virtually to a transformation of the symphysis into an elementary diarthrodial joint. This process is determined by hormonal influences.

3. Diarthroses. Reference to a section through the elbow joint may be used as an example of the diarthrosis. It is noted that the actual articulating surfaces of these bones are covered by a thin layer of hyaline or articular cartilage. Elsewhere, the cavity of the joint is lined with a delicate synovial membrane which is similar in general macroscopic appearance to a serous membrane. The synovial membrane rests on a subsynovial layer of loose connective tissue, and outside this the whole joint is enclosed in a capsule of fibrous tissue.

In some joints a varying portion of the adjacent nonarticular surface of the bone may be included within the joint cavity, in which case the synovial membrane extends over it from the margin of the articular cartilage for some distance before it is reflected on to the inside of the fibrous capsule, and the latter is attached to the bone at a corresponding distance from the actual articular surface. The synovial lining may also be complicated by the formation of folds which project into the joint cavity and increase the surface area of the membrane.

In other words, a diarthrodial joint is functionally a closed cavity, even though its lining mesothelium is anatomically incomplete.

Diarthroses are classified mainly by reference to the type of movement which they permit. The following varieties may be recognized:

a. Enarthrosis, or ball and socket joint, in which a spheroidal articular surface fits into a corresponding concavity. In no cases are the articular surfaces completely spherical in curvature; the radius of curvature is not identical in all diameters, so that they are to a slight extent ellipsoidal. An enarthrodial joint allows movements in all directions—that is to say, flexion and extension, abduction and adduction, and rotation. A composite movement involving all these elementary movements except rotation is termed circumduction.

b. Condylarthrosis, or condyloid joint, in which the articular surfaces are more conspicuously ellipsoid and which allows flexion and extension, abduction and adduction, but no rotation. Since these momements take place about two axes only, this type is sometimes called a biaxial joint. Examples are found in the wrist joint and the metacarpophalangeal joints of the fingers. Like ball and socket joints, a condyloid joint also allows circumduction.

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tional cell. True cartilage is deposited as a thin film of hyaline substance. The tissue then takes on a honeycomb appearance, and this rapidly changes to the appearance of more mature cartilage by a thickening of the intercellular septa, leading to a wider separation of the enclosed cells.

In young growing cartilage, expansion takes place mainly by surface accretion. It also involves some degree of interstitial growth.

Structures which are normally composed of hyaline cartilage have a tendency to calcify and ossify in old age.

In relatively large masses of cartilage, vascular canals are sometimes found penetrating into the cartilaginous substance from the perichondrium. In human development they appear first in the third month, and by the seventh month all the larger masses of cartilage in the fetus are richly permeated with them. The cartilage canals are formed to meet the nutritional requirements of cartilaginous masses which exceed a certain bulk. There is some doubt as to the mode of development of cartilage canals. However, after they have been formed, the contents of the canals provide the osteoblastic tissue and the vascularization for ossification when this ultimately begins and also determine by their distribution the position where the center of ossification appears.

The growth and nutrition of articular cartilage present certain problems of interest. The cartilage cells at the surface are considerably flattened and present an appearance which is usually taken to indicate degeneration and gradual disintegration. The deeper zone of the cartilage, where it lies in contact with actual bone, is calcified. Proliferation of cartilage cells, therefore, presumably occurs in the intermediate zone in order to compensate for the continual wearing away of cartilage at the surface. This attrition is less extensive than might at first sight be supposed, for the articular surface is protected by a thin film of synovial fluid which serves as a very efficient lubricant. The proliferation of cells in mature cartilage probably takes place by amitosis.

Cartilage is an elastic, avascular tissue with a low ratio of cells to matrix. Its chief, if not sole, source of nourishment is the synovial fluid. The mechanism by which nutritive material gains entrance has not been established. The low oxygen requirement and limited reparative ability confirm the fact that cartilage is a relatively inactive tissue.

The nutrition of the central area of articular cartilage may theoretically be derived from two sources, the synovial fluid and the blood vessels in the subjacent bone. If the latter takes any part at all in this process, it must be to an almost insignificant extent, for, as already noted, there is a zone of calcified cartilage covering the bone and this could hardly permit the diffusion of nutrient material. It is generally agreed, in fact, that the cartilage derives its nourishment—probably entirely—from the synovial fluid.

It appears that, from the biochemical point of view, synovial fluid is quite adequate for maintaining the nutrition of articular cartilage and that this is certainly the case is proved by the observation that isolated fragments of cartilage, which have been detached by injury and lie free in a joint cavity, may not only survive but continue to grow.

c. Saddle-shaped joint, or joint of reciprocal reception. In this type of joint the articulating surfaces are each concavoconvex in opposite directions, and the movements which can take place between them are rather complicated. Like a condyloid joint, it allows flexion and extension, abduction and adduction, but the curvature of the articular surfaces also permits a slight rotatory movement. Saddle-shaped joints combine considerable strength with fairly free mobility. One of the best examples of this variety is the carpometacarpal joint of the thumb.

d. Ginglymus, or hinge joint, which allows movement only about a transverse axis—i. e., flexion and extension. The articular surfaces are trochlear or pulleylike in shape. Examples of this type are the elbow joint and the interphalangeal joints.

e. Trochoid, or pivot joint, which allows movement only about a longitudinal axis—i. e., rotation. Two pivot joints are found in the human body—the superior radioulnar joint and the joint between the first and second cervical vertebrae. In each case the articulation consists of a peg or disc fitting within an osseoligamentous ring.

f. Arthrosis, or plane joint, in which the only movement is a slight degree of gliding of one articular surface over the other. Movement is further limited by a tight fibrous capsule and frequently also by interosseous ligaments. The articular surfaces are approximately flat or show but a slight degree of curvature. Examples are found in the intercarpal and intertarsal joints.

Not all joints conform to the requirements of one or another of these categories alone; in some more than one mechanism may be involved. The temporomandibular joint is an instance of such a *compound joint,* for it contains two synovial cavities, at one of which a hinge movement occurs and at the other a gliding movement. It is, therefore, termed a compound ginglymoarthrodial joint. The knee joint, similarly, is a complex mechanism involving a combination of movements characteristic of several of the elementary types.

C. CARTILAGE (HYALINE)

1. Origin and Development. The cartilage covering the articular surface of the bones in a diarthrodial joint is usually of the simple hyaline variety, and, in this case, it is to be regarded as a persistent unossified layer of the cartilage from which the whole bone has been developed. When the articular surfaces are formed from membrane bones (e. g., as in the temporomandibular joint), they are found to be covered with a dense layer of fibrous tissue or fibrocartilage. Hyaline articular cartilage is completely avascular and devoid of a nerve supply. After birth it has no covering of perichondrium or synovial membrane, and it forms a smooth, glistening surface which, lubricated with synovial fluid, allows movements to occur with the minimal amount of friction.

2. Growth, Histogenesis, and Nutrition. In the embryo, cartilage appears as a differentiation of mesenchymatous tissue. The mesenchyme cells retract their processes and become more rounded, while an intercellular matrix of clear mucinoid fluid is deposited between them. This is a transi-

one bone to the other. More or less well-defined bands of fibers are usually differentiated as local thickenings of the capsule to form *intrinsic* ligaments which further strengthen the joint and play a part in restraining movements in certain directions. It may be supposed that these ligaments are developed in response to tensional forces which, as has been seen, determine the deposition of white fibrous tissue in accordance with mechanical requirements.

Besides the intrinsic capsular ligaments, the movements of some joints are functionally controlled by *extrinsic* ligaments, which may be quite independent of the capsule—e. g., the coracolclavicular ligaments in relation to the acromioclavicular joint and the coracoacromial ligament in relation to the shoulder joint. Extrinsic contributions to the fibrous capsule may also be made by the tendons of adjacent muscles. For example, an expansion from the semimembranosus muscle of the thigh helps to form the posterior oblique ligament of the knee joint, but the patellar ligament in front of this joint is really the tendon of the quadriceps extensor muscle, in which the patella is developed as a sesamoid bone. Lastly, certain ligaments have been regarded as the persistent remains of tendons left behind after the phylogenetic degeneration or migration of muscles, but it seems doubtful whether such a morphological interpretation has ever survived a close analysis.

2. Functional Arrangement. With few exceptions, ligaments are practically nonextensible, and they are commonly arranged so that they are taut when the joint is in a position of greatest stability—that is, when the articular surfaces are in maximal congruence with each other. In hinge joints which allow only movements of flexion and extension (e. g., the elbow joint or the ankle joint), the capsule is thin and lax in front and behind so as not to impede these movements, while on either side there are relatively strong and well-differentiated ligaments which help to prevent any lateral movement.

Besides true ligaments, textbooks of anatomy describe as "ligaments" certain fibrous bands or synovial reflections which are not functionally concerned with limiting the movements of the joints with which they are related. In this category is the ligamentum teres of the hip joint, a cone-shaped reflection of synovial membrane extending from the central nonarticular area of the acetabulum to the middle of the head of the femur. It is too weak in structure to play the part of a true ligament, and its importance lies in the fact that it often transmits one or two small blood vessels to the head of the femur.

E. MENISCI

1. Types. Certain diarthrodial joints contain disks, or menisci, of fibrocartilage which are interposed between the articular surfaces of the bones. In some cases these are complete, with the result that the joint has two separate synovial cavities and there is no direct contact between the articulating bones—e. g., the sternoclavicular joint and the temporomandibular joint. In other cases the menisci are deficient centrally and annular or crescentic in shape—e. g., the semilunar cartilages of the knee joint.

3. Gross and Microscopic Appearance. With few exceptions, the articular surfaces of bone are covered by hyaline cartilage. Grossly, this is of bluish white, ground-glass appearance. Its structural components are the typical cartilage cells housed in lacunae, an intercellular system of fibrils and the undifferentiated hyaline matrix. The preponderance of matrix over cells is striking. Superficially, the cells are flat and lie parallel to the joint surface. In the subjacent, transitional layer, the cells are irregular and the lacunae larger and grouped together. The cell processes exhibit branchings and form plexuses. In a third zone, the cells are round and large, with wide blunt processes, and arranged in rows perpendicular to the articular surface. The lowermost layer extends to the line of demarcation beyond which the matrix is calcified.

Microscopic examination of a section of cartilage reveals cells commonly arranged in discrete groups of two, three, four, or more which have arisen from the division of a single chondroblast. Each group is enclosed in a "capsule" of more recently deposited matrix which shows up by its deeper staining. Mitosis is the normal mechanism of cell division in immature cartilage, but it seems that in the mature tissue that this is replaced by amitosis.

The interstitial matrix of hyaline cartilage consists of a translucent substance which is resistant to pressure forces and is at the same time quite elastic.

Adult human cartilage is avascular and has not been shown to contain lymphatics or nervous tissue.

4. Reaction to Injury. From the point of view of its reparative power and of its reactions to irritants, articular cartilage may be divided into central and peripheral areas. The latter are in immediate proximity to the vascular synovial membrane, through which they can derive nutriment more readily than the central areas. They are therefore able to react much more vigorously when exposed to injury. Fisher has shown that an experimental lesion in the peripheral area (in an immature animal) is occasionally followed by the active formation of new cartilage. This is partly the result of proliferation of the cartilage cells themselves and partly due to the proliferation and metaplasia of the cells of the synovial membrane which is immediately adjacent. An incision in the central articular area, on the other hand, is followed by no formation of new cartilage—the lesion is simply repaired by the deposition of fibrous tissue.

5. Function. Articular cartilage is the final recipent of all jolts and blows exerted upon the skeleton. The physical properties by which this tissue attains its efficient buffer action have been investigated in vitro and resilience has been found to be a preeminent characteristic. Cartilage is almost completely elastic to frequent intermittent pressures, but continuous compression of the same total strength decreases its expansile power and lengthens the period of recovery.

D. LIGAMENTS

1. Types. The fibrous capsule which encloses a diarthrodial joint is composed mainly of collagenous fibers which, in general, run directly from

and the acetabulum, which is occupied by synovial fluid and part of the acetabular pad of fat. During extension the latter is gradually extruded from the joint. In the knee joint, also, it has been shown that maximal congruence between the articular surfaces (including those of the semilunar cartilages) occurs only at full extension—the position of greatest stability.

The part played by (*5*) ligaments in restraining joint movements depends on the fact that they are inelastic bands disposed in such a way as to be pulled taut at the extreme limit of the movements to which they are functionally related. In the case of the hip and knee joints, this occurs in complete extension. In joints where no movement is possible about one or more axes, the ligaments related functionally to these axes are so arranged that they remain taut in all positions of movement about other axes.

From the practical and clinical point of view (*6*) muscles no doubt provide the most important mechanism for maintaining the stability of joints. They obviously have the great advantage over ligaments in being able, by progressive contraction or relaxation, to keep articular surfaces in firm contact in all positions of the joint.

Certain muscles (sometimes termed "articular muscles") are concerned entirely with maintaining joint stability—that is to say, their purpose is not to effect movements but to limit them. This is the case with very freely movable joints in which firm ligaments would necessarily impede mobility in some directions. In the shoulder joint, the capsule is so loose as to be hardly capable of contributing to its stability. The joint is, therefore, closely surrounded by a group of short muscles which keep the head of the humerus firmly applied to the shallow glenoid cavity of the scapula in all positions and so facilitate the proper action of the main effectors of movement—i. e., the long muscles, such as the pectoralis major, latissimus dorsi, and deltoid.

The action of articular muscles depends on the reflex maintenance and regulation of their tonus, the anatomical basis of which is supplied by afferent nerve fibers from the joint and its neighborhood and from the muscles themselves. In flexion of a joint, afferent impulses initiated by the contraction of the flexor muscles lead to a central inhibition in the spinal cord of the motor neurons which innervate the muscles of the extensor side. The tonus of the latter is thus gradually diminished and they become progressively relaxed as the movement proceeds. Stretching of the capsule and of ligaments also stimulates sensory end organs in these structures, leading to an increased contraction of muscles appropriate for preventing excessive movement. It will be realized that any interference with this reflex mechanism will tend to distort the harmonious cooperation of the articular muscles and to result in defects in joint movement.

G. SYNOVIAL MEMBRANE

1. Origin. In the case of diarthrodial joints, a cleft appears in the articular disc and enlarges gradually to form a joint cavity. The mesenchyme cells lining the cavity become differentiated to form a lining mesothelium—the synovial membrane. Most of the joint cavities in the human body have made their appearance by the tenth week of embryonic development.

2. Origin. Developmentally, they are to be regarded as persistent organized portions of the embryonic articular disks which are found in all diarthrodial joints.

3. Structure. Structurally they are composed of very dense fibrous tissue, with a varying proportion of elastic fibers and occasional cartilage cells, but the latter may be altogether absent.

4. Function. No doubt the menisci compensate for the incongruity of the articular surfaces between which they are interposed, but it is difficult in some cases to see why there should be this incongruity. In the knee joint, the semilunar cartilages seem to serve the purpose of resilient buffers, minimizing the shock of impacts transmitted from the tibia to the femur. It may be noted in this connection, however, that in animals the experimental excision of a semilunar cartilage is followed eventually by its regeneration. This process is the result of a cellular reaction in the synovial membrane, leading to the production of fibrous tissue which forms the basis of a new meniscus.

Another function ascribed to intra-articular menisci is that they have some relation to the type of movement which takes place at the joint.

The fact that, unlike articular cartilage, menisci are supplied with nerve fibers implies the possibility that they have a sensory function, allowing the muscular control of the joint to respond more promptly and with greater precision to rapid pressure changes within the joint cavity.

F. MAINTENANCE OF STABILITY OF JOINTS AND LIMITING OF MOVEMENT

Diarthrodial joints provide the means of movement between one bone and another, but, particularly in the trunk and lower extremity, they must also allow of a temporary stabilization in certain positions for the transmission of weight. A number of factors are concerned with limiting the movements of a joint and maintaining its stability; these are primarily the shape of the articular surface and the action of ligaments and muscles. Other factors which are often mentioned as being concerned with holding joint surfaces in firm contact are (1) atmospheric pressure, (2) cohesion between articular surfaces covered with a thin film of synovial fluid—it is clear, however, that these must be relatively insignificant—and (3) bony eminences in the immediate neighborhood of articular surfaces and irregularities of the articular surface itself, which will obviously play a part in limiting movement. In the ankle joint, dorsiflexion is limited by the fact that the upper articular surface of the talus is broader in front than behind; consequently, as the foot is raised up at the joint, the talus becomes more and more tightly wedged between the tibial and fibular malleoli.

Besides these examples, in joints in which, at first sight, the articular surfaces would seem to permit almost complete freedom of movement in every direction, a close inspection will show that (4) their curvature is such that complete congruence is obtained only in positions in which the greatest stability is required. In complete extension, the articular surfaces become fully congruent, and no further movement in the direction is possible. In other positions there is always a slight space between the head of the femur

endothelium or cuboidal epithelium, but there is no regularity of such patterns and a basement membrane has never been demonstrated. The synovial lining cells have protoplasmic processes which extend both parallel to the surface, where they interlace and anastomose with those of other cells, and into the deeper fibrous layer. The structure of the intima varies [illegible] the membrane.

[illegible] ps are seen lying on the surface. More commonly, the cellular elements are separated from the cavity by collagenous material of varying thickness. Elastic fibers are scare in the intimal layer. In the deeper fibrous stratum, the cells are smaller and have fewer, shorter, and blunter processes. Adipose tissue diminishes in the outer part of the capsule. From both the cellular and the cell-poor areas of the synovial surface, villi of various sizes project into the joint cavity. A well-marked vascular layer of the synovia has been ascertained, and the capillaries were found to extend through the fibrous layer close to the synovial surface. A subintimal and deeper plexus of lymphatics has been demonstrated.

The nature of the cells of the synovial mesothelium is still in some doubt, but, in their appearance and reactions, they are very similar to fibroblasts. In a series of experiments in which a vital dye (trypan blue) was injected into the knee joints of rabbits, it was found that, although histiocytes in the submesothelial tissue assimilated the dye in a characteristic manner, the mesothelial cells (at least in earlier stages) took it up only in small quantities in the form of fine granules. Later they reached more strongly and assumed a vacuolated appearance. Some of them, also, showed phagocytic properties and were found to contain extravasated red blood corpuscles as well as numerous granules of trypan blue. Others, under the influence of the irritation, became detached and set free as desquamated cells in the inflammatory effusion in the joint cavity. In general, under the conditions of these experiments the mesothelial cells maintained their distinctive characters, the latter contrasting with the histiocytes, many of which could be observed to push their way through the mesothelium to reach the joint cavity, where they became heavily laden with the dye.

3. Regeneration. In contrast to cartilage, the articular membrane has a pronounced and undisputed regenerative ability. Key, in a comprehensive study, observed a series of hemisynovectomized knee joints of rabbits up to 104 days. After a primary polymorphonuclear reaction in the fibrin clot, clasmatocytes and monocytes apeared, and organization by connective tissue was usually complete within 6 days. A layer of collagen formed on the repaired surface, beneath which fibroblasts were seen in aggregates. On the tenth day the number of cells in this layer had increased markedly. In the ensuing stage, a diminution of cellular activity paralleled by abundant deposition of collagen was noted. Villi developed, and after about 60 days a nearly normal synovial membrane was present. Restitution had thus taken place from the external or deeper tissues, with little or no growth from the edges. From these and other experimental studies, Key concluded that joint cavities are clefts lined with slightly modified connective tissue cells.

Up to the fourth month of fetal life, a diarthrodial cavity is completely lined with a continuous stratum of mesenchymatous tissue which covers even the articular cartilage. It is from this layer that the synovial membrane becomes differentiated. When, during the fifth month, active intrauterine movements begin, this layer is soon rubbed off the articular surfaces by friction and pressure. At birth, the synovial membrane still encroaches to a slight extent on the margin of the cartilage, but with the development of a greater range of movement at the joints this encroachment disappears.

2. Gross and Microscopic Appearance. The whole of the synovial membrane is concerned in absorption from the joint cavity, but this process occurs most rapidly where it overlies loose connective tissue and where it is reflected over subsynovial pads of fat. The latter are found in many diarthrodial joints, filling out folds and reduplications of synovial membrane. They provide for an increase in the absorptive area of the synovial membrane, particularly since the mesothelium over them is often thrown into small complicated folds which have the appearance of villi.

Subsynovial pads of fat also serve the mechanical purpose of filling up the changing spaces which occur during the movement of a joint. For example, a pad of fat lies opposite the olecranon fossa on the back of the lower end of the humerus. This fossa accommodates the olecranon process of the ulna in full extension of the elbow, but, during flexion, the pad of fat is pressed into it by the overlying triceps muscle. Similar subsynovial pads of fat are found in relation to the coronoid and radial fossae on the front of the lower end of the humerus.

It should be noted that secondary communications may be established between synovial cavities of joints and bursal sacs in the immediate neighborhood. For example, the cavity of the shoulder joint is frequently connected with a bursa underneath the subcapularis muscle through a gap in the fibrous capsule. Similarly, the knee joint almost always becomes continuous with a suprapatellar bursa which is developed independently beneath the quadriceps extensor tendon.

The synovia appears as a substantial membrane of variable thickness, whose inner aspect shows a smooth, glistening surface, particularly where it overlies ligaments, tendons, and menisci, while in other areas it has a dull luster. Plicae, or folds, are numerous, and occasional trabeculations occur, forming partially closed-off compartments. An inner layer, the intima, can be lifted off easily in some parts, but not in the peripheral zone and over the tendons and menisci, where it adheres firmly. The intima may extend for a short distance onto the marginal cartilage, as it does regularly in human embryos, whereas the outer fibrous layer forms a less complete covering, blending with the perichondrium and periosteum Microscopically, two layers are again distinguishable, but it is readily apparent that there is no definite line of demarcation and that the degree of differentiation is more marked in certain areas. The intimal cells near the articular surface are large, round, or polygonal, with coarsely granular cytoplasm. Their nuclei are oval, and their nucleoplasm shows a chromatin network. The cellular arrangement is single or multilayered, simulating

Proteins, in contrast to small, readily diffusible substances, are removed from joints only by way of the lymphatics.

The removal of particulate matter, such as carbon particles, bacteria, and blood cells, is achieved by a combination of several distinct processes. It takes place more slowly and is less complete than the removal of soluble substances. The increased intra-articular pressure causes a large part of the material to enter directly into the intercellular spaces of the membrane. Another part is removed by connective tissue phagocytes and to a smaller extent by polymorphonuclear leukocytes emigrating from the membrane and carrying the substance back into it. A third part remains in the joint cavity to be ultimately organized. A small portion is taken up by the synovial cells bordering directly on the joint space.

The value of joint exercise, particularly passive, and of massage for increasing absorption from joints has been demonstrated repeatedly. It is probable that the increase is achieved mainly by augmenting the flow of blood and lymph and not merely by elevating the intraarticular pressure.

Experimental studies have shown that *living bacteria* gain access more readily to synovial fluid than to spinal fluid, aqueous humor, and urine. The relatively greater permeability of the synovial tissue as compared with true membranes is again apparent.

6. Alterations in Physiology as Produced by Disease. The changes produced by disease depend on two fundamental alterations in function: (*a*) *Altered permeability of synovial tissue and* (*b*) *disturbance of intra-articular metabolism.* The former permits increased entrance of water, readily diffusible substances, proteins—including fibrinogen—leukocytes, antibodies, and presumably enzymes. The distribution of diffusible substances follows the laws that apply to normal joints. In the case of a utilizable material, such as sugar, equilibrium is established, but, with increased consumption, as in the case of septic joints, the fluid sugar is markedly decreased. The low sugar content in some cases of rheumatoid arthritis, on the other hand, is due, at least in part, to decreased permeability of the membrane to sugar. The amount of protein entering the joint space varies directly with the degree of inflammation. It is slightly greater than normal in traumatic joints and greatly increased in severe rheumatoid and septic arthritis. The proportion of globulin in the entering protein increases as the mebrane becomes more permeable, and, therefore, the albumin-globulin ratio more closely approaches that of serum.

Alterations in the membrane lead also to diminished removal of colloidal and particulate matter. Experimental evidence suggests that this is due to a decreased number of synovial lymphatics. The reduced absorption, combined with greater entrance, may account for the increasing protein concentration and decreasing albumin-globulin ratio in rheumatoid effusions of long duration. The abnormally high concentration of colloidal material raises the osmotic pressure and results in persistence of the effusion.

The altered metabolism of the joint is most apparent in the case of sugar and mucin. Greater utilization of sugar results from various factors: (*1*) *Increased cellular activity of fixed tissue cells;* (*2*) *larger number of leukocytes;* (*3*) *enhanced enzymatic activity; and* (*4*) *bacteria, if present.*

4. Mechanical Properties. The mechanical properties of the articular capsule are determined by its fibrous layer rather than by the intima. As might be expected from its anatomical structure, the synovial membrane has little elasticity. If fresh capsular tissue is tested in vitro, the elastic resistance is about 30 times that of a sheet of rubber of equal thickness. The marked pliability, considered by Danckelmann the outstanding physical characteristic, aids in withstanding the severe stresses of joint motion.

5. Exchange of Substances Through Synovial Membrane. For obvious reasons, the interest of workers has centered on the mechanism of exchange between the joint cavity and the body as a whole: First, because maintenance of the normal state and function of the joint requires entrance of nutritive material and removal of potentially toxic end products; next, because the anatomical structure of the synovialis differs radically from that of the other body membranes across which transfer has been studied, as peritoneum, pleura, and vascular endothelium; finally, because in joint diseases it frequently appears to be this phase of the physiology which is disrupted, early and to a striking degree.

Histological studies show that the joint cavity should be considered a large tissue space. The connective tissue enclosing it, although constituting an anatomical boundary, is not a true membrane, such as the peritoneum, pluera, and the membranes of the choroid plexus and glomerulus. The contents of the articular cavity are presumably in direct communication with the matrix of the synovia tissues. Therefore, it can be assumed that exchange of substances between the vascular or lymphatic system and the synovial fluid involves the same processes as those governing the exchange in any connective tissue fluid. Such transfer necessitates passage through an endothelial wall as well as diffusion through the intercellular spaces of the synovial membrane. In the case of synovial membrane, the term permeability implies these two processes and will be used in this sense throughout the following presentation. Such permeability will be regulated by various physiochemical factors. It will depend on (*a*) *The capillary and lymphatic permeability;* (*b*) *the charges of the diffusing substances; and* (*c*) *any oxidation-reduction potentials involved.* It will also be subject *to the laws of equilibrium across a semipermeable membrane as formulated* by the Gibbs-Donnan theory. The concentration of synovial fluid constituents will vary with their concentration in the plasma and will be influenced by the metabolic activity in the joint cavity.

Readily diffusible substances of small molecular dimensions in homogeneous solution are removed from joints primarily by way of the subsynovial blood capillaries, as shown by the investigations of Rhinelander, Bennett, and Bauer.

Permeability of the synovial membrane to substances of large molecular size, such as proteins, is of special significance in the physiology of joints because of their effect on osmotic pressure, and, thereby, on water exchange. The entrance and removal of colloids involves a more complex mechanism than the exchange of readily diffusible small molecules. The presence of albumin and globulin in normal synovial fluid indicates presumably that the capillaries are slightly permeable to proteins.

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Greater metabolic requirement for sugar, coupled with decreased supply, may lower the fluid sugar to a level insufficient for adequate nutrition of cartilage. In the case of mucin, both formation and destruction are affected. Infectious fluids show a decreased concentration of mucin, a reduced viscosity, and an atypical precipitate with acetic acid. The similarity of these changes to those produced by the bacterial enzyme mucinase suggests that increased destruction of mucin takes place rather than decreased formation.

H. SYNOVIAL FLUID

1. Origin. Many theories concerning the origin of synovial fluid have been proposed and will be presented in brief.

a. Synovial fluid is a product of glandular synovial membrane cells.

b. Synovial fluid is a mixture of the products of disintegration of synovial membrane and a transudate from the capillaries and lymphatics.

c. Synovial fluid is formed from the products of attrition of cartilage.

d. Synovial fluid consists of substances elaborated by synovial membrane cells with the addition of a transudate from the capillaries and lymphatics.

e. Synovial fluid is the liquid matrix of the connective tissue lining an enlarged tissue space, the joint cavity.

f. Synovial fluid is a dialysate from the blood capillaries. Except for the presence of mucin, albumin, and globulin, it could, therefore, be considered a diffusate or a simple ultrafiltrate of serum.

The distribution of electrolytes and nonelectrolytes between serum and normal synovial fluid is in accord with the concept that normal synovial fluid is a dialysate is equilibrium with blood plasma. This relationship is also suggested by the marked vascularity of the synovial intima, whose numerous capillaries and venules are in close proximity to the articular lumen. Such a theory explains all known facts of the physical and chemical composition of synovial fluid except the presence of albumin, globulin, and mucin. The presence of albumin and globulin can be ascribed presumably to slight capillary permeability to protein as previously discussed. The presence of the mucin, whether formed by the surrounding connective tissue, as seems most likely, or by cartilage, in no way invalidates the theory.

Little is known concerning the source of synovial fluid mucin.

The high colloidal osmotic pressure and the high calcium concentration of the synovial fluid form the only essential differences between the synovia and other fluids with the composition of plasma dialysates. These properties of joint fluid are presumably due to the presence of mucin and indicate that mucin plays a role in the exchange of water and other substances between the vascular system and the joint cavity. The finding of similar, if not identical, mucins in subcutaneous tissue and synovial membrane suggests that mucin may have a similar action in all connective tissue fluid.

2. Function. The functions of synovial fluid are partly those inherent in its position as intercellular connective tissue fluid and partly those associated with the specialized functions of joints. It is the main source of nourishment for the avascular articular cartilage and aids also in the nutrition of the superficial cells of the synovial membrane, particularly in villi without blood supply. Bordier suggests that it may act as an important

cohesive force in the joint. The significance of synovial fluid as a lubricant has been generally acknowledged.

3. Cytology. Normal joints contain varying amounts of synovial fluid. The average quantity obtainable from a normal human knee joint is 0.45 cc., with a minimal-maximal variation of 0.13 to 2.0 cc.

Therefore, it seems reasonable to assume that the variations in total number of cells and individual cell types encountered in normal synovial fluid probably represent the intra-articular response to the inconstant trauma incident to daily use. It is of further interest that the highest cell counts are observed in those joints showing the greatest wear and tear changes in consequence of increasing age and long-continued use.

Since synovial fluid serves chiefly as a lubricant for the articular surfaces and as a source of nourishment for articular cartilage, it is not surprising that it contains relatively few cells.

4. Physical Characteristics. Complete physical and chemical characterization of normal synovial fluid has been possible in cattle, and normal human fluid has been compared in enough cases to indicate that the fluids are essentially alike. Normal synovial fluid is a clear, pale yellow, viscous liquid. The average specific gravity of cattle synovia is 1.010, with a maximum of 1.012 and a minimum of 1.009. The relative viscosity of normal synovial fluid varies widely in different joints. The factor responsible for the high viscosity appears to be mucin. Following precipitation of the mucin, the viscosity of the fluid approaches that of water.

5. Protein Constituents. The average concentration of protein, not including the mucoprotein, is 0.88 gm. per 100 cc. in cattle fluid, in contrast to 7.40 gm. per 100 cc. in the serum. This figure is in the same range as that found for normal human synovial fluid. Judging from the findings in a large number of normal and pathological fluids, we would conclude that the value of 3.15 percent represents an abnormal fluid.

In addition to albumin and globulin, synovial fluid contains mucin. It is this mucoprotein that is responsible for the high viscosity and presumably for the lubricating value and high colloidal osmotic pressure of the fluid. The average mucin concentration in normal human fluids obtained in this laboratory is 0.85 gm. per 100 cc., with variations from 0.55 to 1.10 gm.

The exact chemical composition of synovial fluid mucin has not been established. It has been generally accepted that it is a glycoprotein and not a nucleoprotein as originally suggested by Hammarsten.

Normal synovial fluid contains no fibrinogen, as suggested by its failure to clot.

6. Distribution of Nonelectrolytes. The average distribution ratios for urea, uric acid, and nonprotein nitrogen are slightly below 1.00; in individual cases, equal concentrations in fluid and serum have been observed. It is evident, therefore, that these nonelectrolytes are completely diffusible through the membrane separating fluid and serum.

In summary, the distribution of nonelectrolytes is consistent with that found in a dialysate of blood plasma.

7. Hydrogen Ion Concentration. The average pH of normal human fluids obtained post mortem is 7.40.

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III. VERTEBRAL COLUMN

A. EMBRYOLOGY

1. Normal. Although the exact origin of the notochord is not well-established, it seems probable that it originates from a thickening of the *entoderm* in the midsaggital plane at a very early age. This ridge is known as the *chordal plate.* The chordal plate is gradually pinched off from the entoderm, becoming then the notochord.

There is a migration of mesenchymal cells from the *sclerotomes* to surround the newly formed notochord. In the human embryo of *10 mm.* (*5 weeks*), there is a division of the cells surrounding the notochord into segments by the *intersegmental arteries.* At this time each segment is divided into a *light cephalic mass* and a *darker caudal mass.*

In the *14.7 mm.* embryo (*6½ weeks*), the notochord is unchanged. The cells of the cephalic end of the darker caudal mass have not added cytoplasm, because they are farthest removed from the intersegmental artery. These undifferentiated cells constitute the *anlage of the intervertebral disk.* Above the intersegmental artery the remainder of the cells of the *darker caudal mass,* together with the cells of the *lighter cephalic mass below the intersegmental artery,* have added cytoplasm and merged to become the *anlage of the vertebral* body.

In the embryo of *21 mm.* (*7½ weeks*), the cells forming the anlage of the vertebral body have further added cytoplasm, but as yet there is no intercellular matrix. This is known as the *precartilaginous vertebra.* The notochord cells have been "squeezed" or have migrated from the vertebral to the intervertebral region. The cells of the intervertebral disk anlage are becoming elongated to resemble fibroblasts.

In the *57 mm. embryo* (*10 weeks*), the vertebra has become entirely *cartilaginous* with only the *mucoid streak* remaining as a remnant of the *notochord.* The notochord cells are found only at the intervertebral area. Here they are surrounded by futher differentiated cells from the intervertebral disk, forming a fibrocartilage envelope about the notochord cells, separating them from the cartilaginous vertebrae. The intervertebral cells have further differentiated so that the annulus fibrosus can be identified.

In the *157 mm. embryo* (*18 weeks*), the *cartilaginous vertebra shows advanced ossification centers* which obliterate the mucoid streak as they progress. The notochord cells are fewer, and there is a large quantity of mucoid material within the fibrocartilage envelope. From this envelope fibroblasts are invading the mucoid material. *Thus it may be seen that the nucleus pulposus, at first composed of notochord cells alone, is gradually undergoing invasion by fibrocartilage cells from the fibrocartilage envelope.*

8. Distribution of Electrolytes. The concentrations of chloride and bicarbonate are higher in the fluid than in the serum of cattle, whereas the concentrations of sodium, potassium, calcium, and magnesium are lower in the fluid than in the serum. The concentration of total inorganic phosphate is practically the same in fluid and serum.

This is in accord with the results of experiments on mucin previously discussed, which indicate that the base-combining power of mucin is high.

The distribution of electrolytes agrees, in general, with that expected from the Gibbs-Donnan theory of membrane equilibrium and with the results obtained by Greene and Power in the study of the "in vivo dialysate" and by various workers in the study of other fluids which have the composition of dialysates.

come a wedge as soon as weight bearing occurs. Bilaterally occurring half vertebrae may involve large segments of the spinal column as wedged hemivertebrae at different levels. They are placed one on each side and will give in later life a scoliotic curve.

Ventral and dorsal half vertebrae are rare. The explanation for them must be on the basis of faulty vascularization and agenesis of either the anterior or the posterior center of ossification. The malformed vertebral bodies will, at times, take the form of wedges as soon as weight bearing is started.

Congenital weaknesses of the cartilage plates occur in areas where the cartilage plates are penetrated by vessels from the vertebrae, mostly along the peripheral two-thirds and in the center where the axial vessels accompany the notochord. In such areas chondrification gaps may develop. These areas form points of lessened resistance to the increased turgor of the nuclear material, and, at times, the latter will be forced through these gaps to form *spongiosal prolapses.* If this occurs during the actively growing state of the adolescent period, the process will be a rather gradual one stimulating considerable cartilage formation, but little reactive bone.

Multiple spongiosal nuclear prolapses with juvenile kyphosis in the young adolescent groups occur mostly in boys. Schmorl and since then others have examined, at autopsies, numerous spines of adolescent patients with juvenile kyphosis, and they found large nuclear prolapses into the spongiosa through the cartilage plates. These prolapses are in a location which is usually the one where some of the chondrification gaps have occurred owing to degenerated vessels producing weak points. It also has been proved fairly conclusively that the ring epiphysis has nothing to do with the growth in the height of the vertebral bodies. *This growth in the height is exclusively a function of the cartilage plate which is central to the ring epiphysis and underlies the rim ledge proper.* Nuclear prolapses of juvenile kyphosis often occur all along the vertebral bodies of the lower thoracic and upper lumbar region. The uneven growth in height of individual vertebrae tends to retard the growth anteriorly where the increased pressure load is concentrated. More normal growth occurs posteriorly. Thus, the relative wedging of the vertebral bodies is secondary to the improper mechanical function of the degenerating narrowed intervertebral disk. In this way the kyphotic deformity results. The fragmentation of the anterior portion of the ring epiphysis seen in X-ray pictures results from improper motion, abnormal pressure relationship, and shearing stress put upon the anterior annulus fibers and the unfused ring epiphysis.

B. ANATOMY

The average length of the vertebral column in the male is 71 cm.; in the female, 61 cm. *The cervical and lumbar curves are convex forward, the convexity being due to the greater anterior than posterior thickness of the cervical and lumbar intervertebral disks.* These two curves are not present until the holding up of the head and the assumption of the upright posture by the child in walking produce them.

1. Vertebral Body. *The thickness of the vertebral bodies increases downward from the second cervical to the first thoracic, diminishes slightly*

The annulus fibrosus is becoming better developed, connecting firmly the adjacent bodies of the cartilaginous vertebrae.

In the *200 mm. embryo (24 weeks)*, ossification has further obliterated the mucoid streak, remnant of the notochord. *The cartilaginous vertebra is divided by the ossification center into two cartilage plates.* Enchondral bone formation extends across the entire bone end above and below. Of the same structure and origin as the cartilage plate, the epiphyseal ring can be identified anteriorly and laterally. *The nucleus pulposus has undergone further fibrous invasion from the fibrocartilage envelope, and the notochord cells are fewer.*

In the *full-term fetus*, the chief change is in the nucleus pulposus, where the mucoid material is further invaded by fine strands of fibrocartilage. *Fibrocartilage cells are now found interspersed throughout the nucleus pulposus. Notochord cells are found, but they are inconspicuous.* This invasion by fibrocartilage continues throughout life and constitutes the means of growth of the nucleus pulposus. With advancing years, notochord cells become increasingly difficult to find.

Until birth the ossified portion of the vertebra has remained well-rounded where it joins the cartilage plate and its epiphyseal ring above and below, giving the body a biconvex appearance. Ossification proceeds from the entire rounded surface. Gradually the growth of bone alters so that the flattened, adult type of vertebral body is attained.

The next change of consequence is the closing of the epiphyses with the formation of the bony epiphyseal ring, occurring between the ages of 17 and 25 years. Until this period growth has continued by enchondral bone formation over the entire ends, upper and lower, of the ossified portions of the vertebral bodies. This is entirely similar to the growth of the diaphysis in any bone in which the epiphyses have not closed. *The important point of difference is that the epiphyses of the vertebral bodies do not close in their entirety, but growth ceases with the formation of the bony epiphyseal ring. Ossification centers form in the anterior and lateral portions of the cartilaginous epiphyseal ring; then bone growth proceeds until this ring becomes joined to the body of the vertebrae.*

2. Congenital Defects. *In congenital synostosis (block vertebrae) there is complete or partial congenital bony fusion of two or more vertebral bodies* without evidence of any or only small amounts of interposed intervertebral disk tissue. This may be on the basis of complete chondrification of the dense mesenchymal zone which would normally form the annulus fibrosus.

In sagittal cleft vertebrae persistence of the ventrodorsal extension of the perichordal sheath with or without the persistence of the chorda or splitting of the notochord in this area may prevent fusion of the laterally situated cartilaginous vertebral halves. Each half may become ossified separately by its anterior and posterior centers with persistence of the sagittal cleft. With weight bearing in later life, such vertebrae may form the *"butterfly vertebral bodies."*

Lateral half vertebrae or wedge vertebrae, according to Junghanns and others, develop on the basis of *lack of blood supply to the missing half of the body.* At first these half vertebrae are cuboidal in shape, but they be-

herniating, it is torn into various shapes and thicknesses resembling a piece or pieces of fascia, irregular in thickness and contour.

Microscopical examination of the *cartilage plates* reveals true *hyaline cartilage* with a transition to fibrocartilage next to the nucleus pulposus. The *annulus fibrosus* consists of *dense bundles of connective tissue fibers* embedded in a matrix of cartilage which is not prominent except in the inner layers of the annulus fibrosus. The layer of annulus fibrosus to which the nucleus pulposus is attached is the fibrocartilage envelope which constitutes a zone rather than a distinct layer. *The connective tissue fibers in the nucleus pulposus are fine, interlacing in all directions.* In the fluid matrix are found fusiform or spindle-shaped connective tissue cells, groups of cartilage cells, and, occasionally, in young persons, clear vacuolated cells which are thought to be the surviving cells of the notochord. Peripherally the fibrous network gradually becomes dense, finally arranging itself in the thick, curving bundles of the annulus fibrosus.

There is a definite correlation between age and water content of the nucleus pulposus. As independently found by Püschel and by Keyes and Compere, *the water content of the nucleus pulposus diminishes progressively with age.*

In addition to the dehydration of the nucleus pulposus with advancing age, there are other alterations. *In the third decade the fibrous invasion of the nucleus pulposus continues but does not affect the elasticity.* Even at this age it may have a distinct yellow color. *The number of cartilage cells is increased and they occur in larger groups than during infancy and childhood.* In the *fourth decade,* the *elasticity become diminished* by more fibrous invasion. The *nucleus pulposus* is now *tougher and less fluid.* During the *fifth decade,* whorls of fibrous tissue can be found in the nucleus. With *advancing years,* there is *some obliteration of the cellular elements, which appear degenerated.* The fine fibrous structure tends to become more amorphous and finally appears only as a diffuse pink-staining hyaline matrix. In the *senile intervertebral disk,* a brown pigment of unknown nature discolors the nucleus pulposus to varying degrees.

WATER CONTENT OF THE NUCLEUS PULPOSUS AT DIFFERENT AGES

Age	*Püschel* (*Percent*)	*Keys and Compere* (*Percent*)
Full-term fetus	88	88
12 years		80
18 years	80	
72 years		70
77 years	69	

C. PHYSIOLOGY

Since the intervertebral disk serves a purely mechanical purpose, it is probably capable of maintaining its structure upon a very *low rate of metabolism. Although there is a blood supply to the disk until after adolescence, from the third decade on, the nourishment of the intervertebral disk comes from the bone marrow by diffusion through the cartilage plates.* The vascu-

in the next three vertebrae, and then increases progressively until the sacrum is reached. The vertebral canal is large and triangular in the cervical and lumbar portions, where movement enjoys the greatest freedom; small and oval in the thoracic region where motion is more limited.

The vertebral bodies are articulated by means of *amphiarthroses* or slightly movable articulations of the *symphysis* type.

The *anterior spinal ligament* forms a broad band upon the anterior surface of the vertebral bodies extending from the axis to the sacrum.

The *posterior longitudinal ligament* lies within the vertebral canal upon the posterior surfaces of the vertebral bodies. It is broader above than below and *thicker in the thoracic than in the cervical and lumbar regions.* It broadens at each intervertebral disk with which it is intimately blended, being much narrower between.

The *ligamenta flava* are attached to the anterior surfaces of the laminae above and to the posterior surfaces and upper margins of the laminae below. Their thickness increases progressively from the cervical through the lumbar region. At each interlaminar space from the third lumbar vertebra to the sacrum the thickness varies between 2 and 7 mm. *The ligamentum flavum and intervertebral disk form a groove occluding the lower half of each bony intervertebral foramen.*

2. Intervertebral Disk. *The cartilage plates,* which are composed of hyaline cartilage, are cemented to the intervertebral surfaces of the vertebral bodies above and below by a thin layer of calcified cartilage. There is a very thin cortex on these intervertebral surfaces, and, in many places, the bone marrow may reach the surface of the cartilage plates through openings in the spongy bone. The margin of the vertebral body, except at its posterior extremity, is formed by the bony epiphyseal ring. The cartilage plate abuts the bony ring anteriorly and laterally, but, posteriorly, where the ring is defective, the cartilage plate extends to the margin of the vertebral body. On the intervertebral face of each hyaline cartilage plate is a fibrocartilaginous layer, intimately blended with it. This layer separates the nucleus pulposus from actual contact with the hyaline cartilage. The cartilage plate is the unossified remainder of [illegible]

b[illegible]

cartilage plate.

The nucleus pulposus in the adult is contained in a fibrocartilage envelope. This is not a distinct layer but merges with the annulus fibrosus which encloses the nucleus peripherally. This fibrocartilage envelope also separates the nucleus pulposus from the hyaline cartilage plates above and below. The nucleus pulposus is not free within the boundaries mentioned but is rather formed by the interlacing fine fibers which extend from the fibrocartilage envelope. These fibers are interspersed with cartilage cells which occur frequently in pairs or tetrads. The gelatinous matrix in which these structures are embedded was originally the mucoid material from the degenerated notochord cells.

In *consistency* the nucleus pulposus is a moderately tough but very plastic tissue which can be shaped easily between the fingers. In the process of

In the *diagnosis* of metastatic carcinoma of the spine it must be remembered that in most cases the *lesions are multiple.* Roentgen examination of the entire skeleton is often necessary. A careful search for a primary focus must be made, the most important sites being the *breast,* the *prostate,* the *cervix,* the *thyroid,* the *esophagus,* and the *lung. As regards the roentgenological picture, the tendency of metastatic carcinoma of the prostate to cause osteosclerosis is the only consistently recognizable feature.*

b. Tumors of Generalized Distribution. Multiple myeloma is a tumor of adult life, the period of its greatest incidence being the sixth decade. The pain in 70 percent of all cases begins in the lumbar and in the sacral region.

The *roentgenogram* is often diagnostic. The lesions are *rarefied punched-out areas* and *commonly produce pathological* fractures. They are *multiple* or become multiple in more than 95 percent of cases. At times the punched-out areas may be seen in the vertebrae, but more frequently there is a pathologic fracture. Sacral lesions show the characteristic defects in the roentgenogram.

Because of the age at which its onset occurs and the multiplicity of its lesions, *multiple myeloma is difficult to distinguish from metastatic carcinoma.* The following points are useful: *Metastatic carcinoma is by far the more common. The roentgen picture of multiple myeloma is the more distinctive.* The fact that *Bence-Jones bodies* are present in the urine is in favor of a *diagnosis of multiple myeloma,* and their absence suggests a diagnosis of metastatic carcinoma, though they may or may not be present with either condition. The presence of *chronic nephritis,* with nitrogen retention and *high serum proteins,* is definitely favorable to a *diagnosis of multiple myeloma.* Biopsy is the last resort. *Roentgen therapy is the treatment of choice for both conditions.* The lesions of *multiple myeloma respond more rapidly* than do those of metastatic carcinoma.

Hodgkin's granuloma, lymphosarcoma, myeloid tumors, and the *xanthomatous lesions* are rare.

c. Benign Primary Tumors. Among benign tumors, the commonest are *giant-cell tumor* and *osteochondroma.*

The roentgenological picture of giant-cell tumors is variable. As with tumors of the long bones, the other lesions with which giant-cell tumor may be confused are *hemangioma* of the bone and *chondroma. Chondroma* usually may be excluded because of its *rare occurrence in the spine. Hermangioma* has the appearance of giant-cell tumor when the neutral arch or its processes are involved. Hemangioma of the vertebral body, however, has a *very characteristic appearance.*

Benign exostoses, which are common in the remainder of the skeleton, are next in frequency.

The roentgenologic picture of this tumor is typical of osteochondromas elsewhere.

Chondroma of the spinal column is rare.

Bucy and Capp pointed out that, when the vertebral bodies are involved with *hemangioma, vertical striations* are produced which form an easily recognized roentgenologic picture. When a hemangioma involves a *flat*

lar bed of the bone marrow reaches the cartilage plates at the many points where the spongy bone reaches the surface, uncovered by a cortical layer. Nutrition may come also from the plexus of vessels of the periosteum and spinal ligaments in close apposition to the annulus fibrosus. Probably the complete avascularity of the mature intervertebral disk accounts for its early decadence and feeble reparative efforts.

The *nucleus pulposus is incompressible* and, owing to its plastic nature, *obeys the laws of fluids.* It is the tension of the elastic annulus fibrosus which keeps the nucleus pulposus under pressure, even when the intervertebral disk is not bearing weight.

The *annulus fibrosus* can be compared to a strong but somewhat elastic membrane firmly binding the vertebral bodies together. The nucleus pulposus, which fills the cavity separating the vertebral bodies, can be compared to a fluid. Although the nucleus pulposus is plastic rather than fluid, it behaves as a fluid in the limited degree of displacement to which it is subjected in movements of the vertebral column.

When a *sudden force* is put upon the *intervertebral disk,* the *column of fluid is displaced laterally* in all directions, distending the elastic membrane. *In this way the shock is absorbed.* Much more important than this shock-absorber function, is the equalization of pressure over the entire intervertebral surface of each vertebra. Since the pressure throughout a fluid medium is uniform, any force transmitted thus is equally distributed over the intervertebral surface of each vertebral body. Without a fluid center within the intervertebral disk, transmission of force would be perfectly distributed only when the vertebral bodies remained in a straight line.

The annulus fibrosus must resist the pressures which tend to displace the nucleus pulposus. In addition, *it binds the margins of the vertebral bodies firmly together* and thus helps to prevent excessive angulation at a single articulation. It can be seen, then, that the annulus fibrosus has to withstand either *pressure* tending to distend it or *tension* in a direction parallel to the vertebral column. By its anatomical configuration, it is equipped to withstand these forces.

The fluid nucleus pulposus can distribute the transmitted force evenly only when the intervertebral surfaces of the vertebral bodies are moderately flat, allowing it to flow from one portion of the enclosed cavity to another. (The flow is relative rather than absolute since the nucleus pulposus is actually attached to the annulus fibrosus and laminae of cartilage which enclose it.)

D. PATHOLOGY

1. Tumors of Spine

a. Metastatic Carcinoma. Carcinoma of the *breast* may be considered the *most frequent cause of metastases* to the vertebrae. The condition has no predilection for any particular part of the spine and is *usually an osteolytic process,* though osteosclerosis may be produced.

Carcinoma of the *prostate* is more characteristic in its metastases to bone. It shows a marked tendency to appear in the sacral and lumbar vertebrae and produces a *lesion* which is predominantly *osteosclerotic.*

joints, and oblique and anteroposterior roentgenograms may reveal pathological deviations here. Because the calcium salts remain and help to localize the lesions in pyogenic bone conditions, *atrophic changes do not appear early, as a rule.* As the lesion extends, destructive phenomena are evident. Occasionally, there is a complete or wedge-shaped collapse of the vertebral body. *The intervertebral disks are often destroyed.*

The *most characteristic feature* of pyogenic osteomyelitis is the presence of a *reactive new bone formation* which *produces bony bridging* and is *always present sooner or later in the disease.* This bridging and posterior involvement are the chief differential points in ruling out tuberculosis. *New bone formation is often very extensive and results in fusion of the vertebrae, even relatively early.* In any case of spondylitis which has been studied by serial roentgenograms over a long period, the presence of a localized uniform narrowing of the intervertebral spaces with hypertrophic changes about the margins of the vertebrae, with or without evidence of abscess formation, should suggest the possibility of pyogenic spondylitis. In acute cases small focal destructions close to the disk appear and may rapidly involve the disk, with subsequent narrowing.

As a rule, abscess formation can be easily demonstrated.

The most common and important *complication* of pyogenic osteomyelitis of the spine is *suppuration and the formation of abscesses.* These are characterized by their great size and tendency to gravitate and migrate from their original sites. *Abscesses may form* (1) *in the retrophalangeal space,* (2) *in the retromediastinal space,* (3) *between the iliopsoas muscle and its fascia,* (4) *in the retroperitoneal space,* (5) *in the hollow of the lower sacrum and coccyx which may point in the subgluteal region, perionally or perirectally,* and (6) *there may be invasion of the spinal canal with resultant cord symptoms.*

Other *complications* are *vascular* in nature, such as thrombosis of the iliac veins.

Gibbus formation occurs, but it is not as common as in tuberculosis of the spine.

Spontaneous or postoperative *sinus formation* is not uncommon. In many instances the sinuses are multiple. *Amyloidosis* may occur but is not a frequent complication. *Bony metastases* are of infrequent occurrence.

c. Tuberculosis. In tuberculosis of the spine it is usual to classify the cases as (1) central, (2) epiphyseal, and (3) anterior types.

In the *central type* of disease the infection begins in the interior of the body of the vertebra and spreads through and destroys the cancellous tissue until it reaches the cortex, usually in the anterior portion of the body. The cortex is then penetrated, and tuberculous tissue accumulates beneath the anterior longitudinal ligament, which is stripped up from its attachments to the bone and to the adjacent intervertebral disks. *The disease may thus reach and invade the bodies of the vertebrae above and below without passing through the intervertebral disks.* Likewise, it may erode the posterior cortex to appear beneath the posterior longitudinal ligament, and the tuberculous tissue may penetrate this ligament and spread over or completely encircle the dura at the level of the disease.

bone, such as the sacrum, a *marked sunray* effect is produced in the periosteal zone. They also stated that the affected bone does not collapse and produce pain but that the first symptoms are those of compression of the spinal cord.

d. Malignant Primary Tumors. Malignant primary tumors of the spinal column are less common than benign growths. The frequency of occurrence of malignant primary tumors of the vertebral column are as follows: (1) Osteogenic sarcoma, (2) chondrosarcoma, (3) chordoma, and (4) Ewing's tumor.

In *chordoma* the *roentgenogram* usually shows destruction of bone, with the shadow of a tumor in the soft tissues. The tumor is slow growing but *malignant* and kills by invasion of vital structures. The *microscopic picture* is variable and shows solid cords of polyhedral and globular cells with abundant granular cytoplasm. Some of the cells show vacuolation.

Irradiation seems to have little effect on this type of tumor. *Surgical excision* may be attempted, but *recurrence* is the rule.

In the considerations of tumors of the spine, one must always bear in mind that soft tissue tumors may produce bone changes in the adjacent bones. One must consider and rule out such conditions as sympathicoblastoma, neurinoma, meningeal tumors, neurofibromatosis, glial tumors, and teratologic tumors.

2. Infectious Diseases of Spine

a. Vertebral Lesions in Undulant Fever. Vertebral lesions of undulant fever may be suspected in patients suffering from back pain, who are known to have had the disease recently, or in those who had had some of the symptoms, even though their cases have not been diagnosed as undulant fever.

In the cases recorded in the literature diagnosis was made by the serological and roentgenographic findings, seldom by culture. This is due to the relatively rare occurrence of abscess formation (12.5 percent) and the technicalities encountered in growing the organism.

Diagnostic aids are the *low leukocyte count* and the *elevated temperature* concomitant with the *relatively high sedimentation rate.* Repeated negative tuberculin tests and a negative Widal test are valuable in the differential diagnosis.

Roentgenographic evidence of an *infectious process, characterized by increased density of the vertebrae involved, preservation of the body contour, relatively minor changes in the intervertebral disk, and hypertrophic spurring,* is significant.

The positive agglutination test, opsonic index, and skin test, or the recovery of the organism from the urine, the blood stream, or the abscess are rather conclusive.

b. Pyogenic, Osteomyelitis. Among the *roentgenographic findings,* abnormalities of the intervertebral spaces, however slight, are important. The *trabecular architecture of the affected area becomes obscured in the early stages.* Other changes observed include *sequestration, mottling of the vertebrae,* and varying degrees of *erosion and destructive phenomena.* The most destructive phases of the disease in the intervertebral disk, in the early stages before contiguous bone has been destroyed, are reflected merely by spacial alterations. The lesion may and does begin in the interarticular

Due to the position of the *articular facets,* destruction of the bodies of the vertebrae in the *thoracic region* results in more *extensive collapse* and *more acute angulation* than does an equal amount of destruction in the cervical or lumbar region. But even in the thoracic region, with destruction of the bodies of several vertebrae and marked angulation, the *spinal canal is not narrowed sufficiently to embarrass the spinal cord seriously.* However, if the pedicles and articular facets are destroyed, a *pathological dislocation* may occur and the cord may be pinched by the persisting posterior margin of the vertebra above or below, and permanent total paralysis may occur.



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The central type of disease may cause no symptoms until a considerable portion of the body of the vertebra is destroyed and the bone collapses or until the cortex of the vertebra is perforated and the disease appears beneath the ligaments and causes localized pain. It is evident that this type of disease is *not often diagnosed until considerable destruction is present.*

The *anterior,* or superficial, type of spinal tuberculosis *begins in or near the anterior cortex of the body* and spreads up and down the spine beneath the anterior spinal ligament to *invade and to erode the anterior portions of the bodies of the adjacent vertebrae, without causing much damage to the intervertebral disks* or collapse of any vertebral body until late in the disease.

The *epiphyseal* or *intervertebral articular type* of disease *begins in or near the upper or lower surface of the body and spreads to the intervertebral disk and through the nucleus pulposus to the adjacent vertebrae.* This type of disease *causes symptoms relatively early* and can be diagnosed in the *roentgenogram by the narrowing of the intervertebral space.* This type does not occur in young children, in whom the *cartilage* adjacent to the *intervertebral disk is relatively thick* and *offers a much firmer barrier to the spread of the disease than does the cancellous bone of the vertebral body.*

From pathological studies on seven spines of *children* who had Pott's disease, Compere and Garrison concluded that *the intervertebral* disk was *highly resistant* to destruction by tuberculous granulation tissue.

When the tuberculous focus reaches a certain size, its central portion becomes necrotic and may caseate, but, if the disease is advancing, it tends to liquefy and form an abscess, which increases in size as long as the disease is progressing. The abscess appears beneath the anterior longitudinal ligament and first elevates and then penetrates this ligament and forms a cavity lateral or anterior to the spine. As the abscess enlarges, it follows the *path of least resistance through the surrounding tissues.* Two or more abscess cavities may arise from a single focus in the spine. *Abscesses which arise above the diaphragm tend to remain in the chest cavity or to point posteriorly. Those which arise below the diaphragm tend to enter the pelvis along the sheath of the iliopsoas muscle and may point in the groin or thigh, or they may burrow posteriorly and appear in the lumbar region.*

After the abscess ruptures and discharges its contents or is drained, the tuberculous sinus which persists is vulnerable to infection by pyogenic organisms.

A complication which occurs in about *12 percent* of the patients with Pott's disease is *paraplegia.* The tuberculous granulation tissue may completely surround the spinal cord, being separated from it by the dura. This membrane affords a very firm barrier to the tuberculous tissue and is not invaded by the disease. A pachymeningitis does not occur. Even without mechanical compression of the cord, the presence of active tuberculous granulation tissue in intimate contact with the dura may cause degenerative changes in the cord, which appear to be the result of the *general toxic and vascular reaction* occurring in the vicinity of any active tuberculous focus, and, if this condition persists long enough, the paralysis will be permanent.

age of 20. In any representative series of cases about three-fourths of the patients will be within these age limits. There seems to be a predilection for males over females, approximately in the proportion of 2 : 1. Trauma has often been attributed as an etiological factor. Most authorities tend to reject the idea of a casual relationship between trauma and the appearance of the tumor.

Clinical Aspects. Pain and swelling are the commonest features. In children with severe tumors, loss of weight and anemia are quite common findings.

The time interval between the of onset of symptoms and diagnosis may be several weeks or may be 6 months or more. The tumor metastasizes by the blood stream to the lungs. Early metastases to the lungs are frequent, although the tumor may not be calcified enough to discern roentgenologically.

Location. The commonest site of occurrence is in the lower end of the femur. The next most common site is in the upper end of the tibia, followed third in frequency by the upper end of the humerus. Occasionally, the tumor occurs in the ilium and the upper end of the fibula. The tumor affects long bones and usually involves one end of the shaft and part of the adjacent epiphyseal area. One may occasionally see the tumor invade and develop in the mid shaft.

X-Ray Picture. About one-half of all osteogenic sarcomas are easily recognized. These are the sclerosing ones that form a great deal of new bone. The perforation of the cortex would tend to lead one to believe that a high grade of malignancy is present.

Bone destruction always accompanies new bone formation. It is usually most marked when the tumor begins about the center of a bone and erodes both cancellous and cortical structures in most of its circumference. This produces roentgenologically central reduction in density with ragged and uneven outlines. However, in some cases the tumor may infiltrate cancellous spaces and extend into the periphery, leaving much of the old bone intact. This produces blotchy reduction in density, with large and small cavities throughout the involved area. When it begins along the surface, there is sloping erosion of the outer surface of cortex, which is, in some of its extent at least, usually perforated. If the lesion is bone-destroying, with little or no new bone formation, it is referred to by Godman as *osteolytic osteogenic sarcoma.* If there is associated ossification, the newly formed bone replaces in varying degrees—sometimes extreme—the old bone; but its location and arrangement are different, and it can be detected in roentgenograms. It produces a more or less dense, blurred amorphous shadow.

Pathology—Gross. In a reported series of osteogenic sarcomas, about one-quarter were relatively slightly ossified, about one-quarter moderately ossified, and one-half heavily ossified and considerably eburnated. On the whole, the less ossified the tumor, the most likely it is to show considerable necrosis, cystification, and telangiectasis as secondary features of its pathological anatomy. However, even highly ossified tumors occasionally show considerable telangiectasis, particularly in their more peripheral portions.

IV. PATHOLOGY

A. CLASSIFICATION OF BONE TUMORS

The Registry of Bone Sarcoma defines osteogenic sarcoma as a sarcoma derived from tissue presumably intended to form bone, irrespective of whether it eventually does so.

The term "osteogenic," defined as "originating in bone," has been used by the Committee on Classification of Bone Tumors of the American College of Surgeons.

The American College of Surgeons registry for bone tumors written in 1939 follows:

REVISED CLASSIFICATION OF BONE TUMORS, 1939

American College of Surgeons

	Malignant	*Benign*
1. Osteogenic series	1. Medullary and subperiosteal 2. Telangiectatic 3. Sclerosing 4. Periosteal 5. Fibrosarcoma a. Medullary b. Subperiosteal	1. Exostosis 2. Osteoma
2. Chondroma series	1. Chondrosarcoma 2. Myxosarcoma	1. Chondroma
3. Giant-cell tumor	Benign, malignant	Epiphyseal giant-cell tumor
4. Angioma series	1. Angioendothelioma 2 Diffuse endothelioma	1. Cavernous angioma 2. Plexiform angioma
5. Myeloma series	1. Plasma cell 2. Myelocytoma 3. Erythroblastoma 4. Lymphocytoma	
6. Reticulum cell lymphosarcoma		
7. Liposarcoma		

It should be stressed that a biopsy should be made to ascertain the correct diagnosis of all bone tumors and lesions of dubious nature.

It will be noted that osteogenic sarcoma has been subclassified into many groups. However, in many laboratories a subclassification is not made; either it is osteogenic sarcoma or it is not. There is no essential difference insofar as their basic nature is concerned.

Osteogenic Sarcoma. Osteogenic sarcoma is the commonest of the primary malignant tumors of bone. The tumor is most common in childhood, adolescence, and early adult life, and more than one-half occur before the

An osteochondroma which has undergone transformation into a chondrosarcoma presents a dense, blotchy appearance over a considerable area, usually associated with the presence of more ragged, irregular radiopaque streaks extending away from the main part of the lesion.

DIFFERENCES BETWEEN CHONDROSARCOMA AND OSTEOGENIC SARCOMA

Chondrosarcoma	*Osteogenic sarcoma*
1. Less common.	1. More frequent.
2. Occurs at a much later age.	2. Occurs at an earlier age.
3. Runs a much slower course.	3. Runs a rapid course.
4. Metastasizes to lungs later.	4. Metastasizes to lungs early.
5. Develops out of full-fledged cartilage.	5. Issues from bone forming mesenchyme
6. Never shows neoplastic osteoid tissue and bone evolving directly from a sarcomatous stroma. The basic proliferating tissue of the tumor is full-fledged cartilage.	6. [illegible] osteoid tissue and bone.

The microscopic characteristics of malignancy are: (1) Many cells with plump nuclei; (2) more than an occasional cell with two such nuclei; and, especially, (3) giant cartilage cells with large single or multiple nuclei or with clumps of chromatin.

In regard to many chondrosarcomas, it is possible, from the clinical course and the roentgenographic and pathologic findings, to show or deduce that they have arisen in lesions originally benign. Thus a chondrosarcoma not uncommonly issues from a solitary benign enchondroma (benign central chondroma), especially of a long tubular bone. Again, a chondrosarcoma occasionally develops out of the cartilaginous cap of a solitary osteocartilaginous exostosis (so-called osteochondroma), perhaps more commonly of a flat bone or a vertebra than of a long bone. Analogously, a chondrosarcoma may grow from one of the numerous lesions in skeletal enchondromatosis or in multiple osteocartilaginous exostoses. A chondrosarcoma which begins its development within the interior of a bone may be denoted as a *central chondrosarcoma,* and one which begins in the cartilaginous cap of an osteochondroma as a *peripheral chondrosarcoma.*

Eventually, in a fully developed chondrosarcoma, central or peripheral, the neoplastic tissue is richly cellular. In addition, it shows striking irregularity in the size of the cells and their nuclei, the presence of numerous plump cells with multiple nuclei, pronounced hyperchromatism of the nuclei, and the presence of many uninuclear giant cells.

Not too much importance should be attached to the scarcity or even absence of mitotic division figures. If attention is concentrated upon these, one may miss the diagnosis, since cell division in chondrosarcomas tends to be amitotic.

Alteration in the character of the cartilage matrix—that is, change from hyaline to myxoid or mucoid—is not a particularly significant element in the composition of chondrosarcoma.

The presence in a cartilaginous growth of some, or even considerable, calcification and ossification is not inconsistent with its being a chondrosarcoma.

Microscopic. In a given lesion, the still unmodified stromal tissue may be composed predominantly of spindle-shaped cells or may be definitely anaplastic and present a highly polymorphous cellular character. Scattered and focal deposition of calcium in the collagenized stroma then inaugurates the appearance of actual tumor bone. If the tumor is one whose sarcomatous stroma does not lay down much tumor osteoid and bone, the original osseous tissue (both spongy and cortical) at the site of its growth is subjected from the beginning mainly to resorption and dissolution. If the lesion is one whose sarcomatous stroma does lay down much tumor osteoid and bone, the highly sclerotic and eburnated areas in the interior of the affected bone part are found to result from superposition of ossified tumor tissue upon the pre-existing spongy trabeculae, with consequent obliteration of the spongy marrow spaces.

Prognosis and Treatment. Osteogenic sarcoma is a tumor having an extremely high mortality rate, no matter how the case is treated. The 5-year survival rate is no more than 10 percent.

Osteochondroma. The pathology of an exostosis or osteochondroma is the same as that described under the individual tumors of multiple hereditary exostoses. The tumor itself is the *commonest benign tumor.* The tumor occurs at the metaphyseal end of a long bone, varies in size and shape, and is capped by hyaline cartilage. The bone beneath the cartilage is spongy and is continuous with the spongy portion of the main bone. Growth of the tumor occurs by endochondral ossification. (For multiple hereditary exostoses see "Systematized Anomalies of Skeletal Development.")

Chondrosarcoma

Etiology. Unknown.

Age, Sex, and Localization. In the great majority of cases the patients are between 30 and 50 years of age, equally divided between the sexes. Long tubular bones, the innominate bones, and the ribs are the commonest sites. Trauma is not a factor.

Clinical Findings. Patients have a long history. Histories tend to be longer in cases of peripheral chondrosarcoma.

Extension and Metastasis. Chondrosarcomas (central or peripheral) are likely to remain only locally invasive for years. When a chondrosarcoma finally metastasizes, the tumor tends to break into the regional venous channels and, by intravascular growth and extension, may reach the heart and lungs. Metastases elsewhere than in the lungs are uncommon in connection with chondrosarcomas.

X-Ray Findings. A long bone presenting an irregularly mottled and calcified shadow in its interior and a fuzzy area of localized destruction of the cortex should make one suspect tumor of this type. This suspicion is all the more justified if, where the cortex is undergoing destruction, it is somewhat thickened in part or throughout and is overlaid by tissue casting an abnormal shadow.

In the absence of mottling and calcification as a clue to the cartilaginous nature of a central bone lesion, it will not be clear at all that a given malignant tumor in the long bone is a chondrosarcoma.

Metacarpal and Metatarsal Bones. The X-ray findings are essentially similar to those of the phalanges. In the metacarpal and metatarsal bones the enchondroma tends to be more in the distal part of the shaft. A solitary focus of fibrous dysplasia may occur in a metacarpal or a metatarsal bone and may simulate an enchondroma. A squamous epithelium-lined inclusion cyst apparently does not occur in a metacarpal or metatarsal bone.

Long Bones. The findings in the metacarpals and phalanges are applicable to the long bones. The presence of spotty or blotchy calcification points rather definitely in the direction of an enchondroma. In the absence of radiopaque spots, the diagnosis of enchondroma cannot be made with any confidence. Again, fibrous dysplasia and solitary bone cyst must be considered in the differential diagnosis.

Pathology. The fragments of cortical bone are thin and even shell-like if they come from an affected area where the cortex has been bulged out, as it commonly the case when the lesion is in a phalanx or a metacarpal or metatarsal bone. On the other hand, the cortical fragments may show but little thinning or none if they come from a lesion which has failed to bulge the cortex, a state of affairs not uncommon when a long tubular bone is affected. The medullary surface of the cortical fragments, whether they are only slightly or greatly thinned, usually shows some erosive ridging and grooving. The periosteal surface is ordinarily found smooth and without evidence of apposition of new bone unless the cortical fragments have come from a site of recent infraction.

Microscopic Findings. In attempting to evaluate the benignity of a cartilage tumor, one should concentrate on the cellular elements, specifically those in the viable and not too heavily calcified areas. The cartilage cells from a representative area will be found consistently small. The nuclei are consistently small and are roundish and dark staining. The cytoplasm is pale and often more or less vacuolated. One may find occasional cartilage cells which, though small, contain two nuclei. Such binuclear cartilage cells are in process of amitotic division, and a clearly benign enchondroma does not show cartilage cells in mitosis.

As already noted, benign enchondroma (especially in a long tubular bone) sometimes undergoes malignant transformation. As a benign growth, the lesion may have been present for many years and may even have been entirely symptomless until there was a change in its nature. Prior to its revivescence and malignant transformation, the enchondroma may even have become extensively calcified and ossified. The evolution of a chondrosarcoma out of a benign enchondroma, though sometimes rapid, is usually an extremely slow process. Early in this evolution cytologic evidence of change in the direction of malignity is already present. However, at this stage, the significant cytologic aberrations are by no means obvious and, furthermore, are usually present only in scattered fields. To recognize them, one has to take due cognizance of the characteristic cytologic pattern of the benign lesion as described and watch for such deviations from that pattern as the presence of more than an occasional binuclear cell and a general plumping-up of the nuclei. If one finds, even only in scattered areas, many microscopic fields showing several or more binuclear cartilage cells, or many cartilage

In a central chondrosarcoma, such areas may be regarded merely as evidence that the growth had been benign in the past and that it had matured and regressed to some extent at some time before undergoing revivescence and malignant transformation. In a peripheral chondrosarcoma, some calcification and ossification of the matrix, at least in the early phases of the growth, are to be expected.

Treatment. The only form of therapy which offers any prospect of cure is surgery. Surgical treatment should be radical.

Irradiation therapy is of no value, since the tumor is highly resistant. However, it may serve as a palliative agent for a chondrosarcoma in an inaccessible site.

Solitary Benign Enchondroma of Bone. A benign cartilaginous growth which begins its development in the interior of an affected bone and involves only a single bone in any one subject.

Etiology. Enchondromas originate from a cartilage rest snared off from an epiphyseal cartilage plate.

Clinical Aspects

Sex and Age. There are no significant sex differences, and the condition may occur at any age.

Location. This tumor has a predilection for the limb bones, especially the bones of the hand. The humerus and femur are the commonly involved long bones. The tumor may also occur in the ribs, pelvic bones, vertebrae, or the skull bones. These are uncommon sites.

Enchondromas of short or long tubular bones begin their development in the metaphysis as a rule. This tumor does not tend to violate the epiphyseal cartilage plate. However, involvement can occur after the epiphysis has fused with the shaft.

X-Ray Findings

Phalanges. The lesion appears as a more or less oval rarefaction shadow. This may be situated centrally within the affected bone and may fail to cause distention of the surrounding cortex. Eccentrically situated enchondromas show a fine radiopaque line where they abut on the uninvolved portion of the phalanx. The rarefaction shadow may present a trabeculated appearance with fine densifications varying in size. These densifications reflect foci of ossification in the cartilage.

Benign enchondroma is by far the commonest solitary lesion affecting the phalanges. In the differential diagnosis, one must consider such conditions as: (1) Solitary bone cyst, (2) giant-cell tumor, (3) osteochondroma, (4) squamous epithelium-lined cyst, and (5) ossifying fibroma.

Solitary bone cyst rarely occurs in phalanges. Rarely in toes.

Giant-cell tumor rarely occurs in the phalanges. Originates in the epiphysis.

Osteochondroma. Squamous epithelium-lined cyst occurs exclusively in terminal phalanges and nearly always in the terminal half of the phalanx, a site which is rare for a benign enchondroma.

Ossifying fibroma is common in the toes. Located in terminal phalanges.

the stromal cells of the tumor arise through proliferation of the mesenchyme-like supporting connective tissue of the marrow. The origin of the multinuclear giant cells is controversial. It must be stressed that the stromal cells are the deciding factor in the diagnosis and grading of giant-cell tumor. Jaffe and Lichtenstein and Portis use gradients of I and II, and III to evaluate the change from benignity to malignancy.

Classification. About 50 percent may be considered benign and do well with a thorough currettement—called grade I.

About 30 percent tend to recur after curettement—called grade II.

About 15 percent become malignant—called grade III.

Supposed Giant-Cell Tumor Variants. (Cf. bibliography of giant-cell tumor.)

1. Spindle cell or osteitis fibrosa variant.
2. Xanthoma variant.
3. Myxomatous variant.
4. Cystic variant.
5. Aneurysmal variant.
6. "Brown tumors" of hyperparathyroidism and giant-cell epulis.

Treatment. The following methods of treatment may be used:

1. Resection.
2. Curettement.
3. Amputation.
4. X-ray in a surgically inaccessible site.

Since giant-cell tumor is a formidable tumor to be reckoned with, it should be completely eradicated.

Epiphyseal Giant-Cell Tumor. Epiphyseal giant-cell tumor is a lesion peculiar to male adolescence. The lesion always starts in the epiphysis and may extend into the diaphysis.

Codman collected nine slowly growing "epiphyseal chondromatous giant-cell tumors of the upper end of the humerus," producing bone destruction with more or less extensive surrounding new bone formation, and in some cases containing blotchy islands of calcification and ossification. The tumors were composed of a mixture of hyaline cartilage, macrophages, fibroblasts, and giant cells similar to those in benign giant-cell tumor.

Codman was particularly interested in the shoulder and reviewed the shoulder bone tumors of the Bone Registry. Actually these tumors are more common in the knee than in the shoulder.

Angioma Series. Several types of endothelial cells are available as sources of tumors in bone, including the lining cells of blood and lymph vessels, perivascular endothelium, sinus endothelium, and cells of the lymphoid reticulum. The vascular endothelium has angioblastic properties and seems to give origin to angioendothelioma. The source of the more cellular tumors is undetermined. While intermediate types of tumors occur, three structural varieties may be recognized: *Angioendothelioma; multiple endothelioma;* and *diffuse endothelioma or endothelial myeloma (Ewing's tumor).* The entire group is characterized by a predilection for the bone shaft, a tendency to multiplicity, a cellular and vascular structure, marked osteolytic properties, *failure to produce tumor bone,* and a relatively slow but fatal course.

cells with plump nuclei, and especially any cartilage cells containing large or multiple nuclei, the growth is no longer a clearly benign enchondroma.

Treatment. The treatment of choice is surgical and consists essentially of curettement and collapse of the distended part of the cortical wall and insertion of bone chips or a solid bone graft.

Giant-Cell Tumor of Bone. Giant-cell tumor is a neoplasm arising apparently from the undifferentiated supporting connective tissue of the marrow and clearly delimitable on the basis of its cytologic details.

Etiology. Unknown.

Sex. Males and females are about equally affected.

Age. After the age of 21.

It is exceedingly rare for the presence of more than one giant cell tumor in the same subject. The usual site of the tumor is an epiphysis or an epiphyseal end of some long tubular bone. However, a giant cell tumor may take origin in a bone which has no epiphyses: i. e., maxilla, mandible, or astragalus. It may also originate in a nonepiphyseal part of a bone: i. e., central part of a vertebral body.

X-Ray. The "typical" X-ray appearance of the epiphyseal end, sometimes alone but more often with part of the adjacent metaphysis, shows a large and somewhat eccentric area of rarefaction. The involvement may extend to the articular cartilage, and occasionally an intra-articular fracture line is present. The bone cortex in the affected region is likely to be found thinned and expanded and may even show fracture. The distended area of rarefaction may be traversed by delicate septa producing a multilocular cystlike effect. Most important diagnostically are the location of the area of rarefaction in the end of the bone, and the thinning and expansion of the cortex, particularly on one side. There is an obvious absence of periosteal new bone formation over the thinned and expanded cortex. A chondrosarcoma or a fibrosarcoma, especially when originating in an epiphyseal end of a long bone, may produce an X-ray appearance resembling giant-cell tumor. It must be stressed that there is no definite set of X-ray findings pathognomonic of giant-cell tumor.

Gross Appearance. The gross appearance of the tumor which has not yet broken its bounds into the surrounding tissues presents the following features. The bone outline is generally found expanded, at least in part. The distended area is usually delimited by a thin shell of bone, over which the periosteum is somewhat thickened. The original spongiosa has been resorbed. The tumor is often found to have extended to the articular cartilage. The cartilage, however, is usually not perforated by tumor tissue. The tumor tissue, which has undergone but little modification, has a rather uniform dark red or reddish brown color and is of fairly firm consistency. The usual color and consistency are often found altered by secondary changes, and the tumor may present evidences of hemorrhagic areas, necrotic areas, and cystic areas. Large blood spaces may also be present in very advanced lesions.

Microscopic Pathology. The tumor consists of a moderately vascularized network of stromal cells and multinuclear giant cells. Occasional stromal cells may present evidence of mitotic division. It is thought that

Ewing's tumor develops in the shaft, perforates the cortex, and forms a soft tissue mass; it occurs in adolescence.

Tumors of the prostate, thyroid, kidney, lung, and breast metastasize to bone. As a matter of fact, any carcinoma can metastasize to bone. The only variable is frequency.

Osteoid Osteoma. Osteoid osteoma, when located under cortex, causes a tremendous production of bone. The tumor is made of osteoid and new bone.

Prognosis of Ewing's Tumor. Patients that run a slight fever, moderate anemia, and rapid sedimentation rate have a more severe course than those without these symptoms. In general, the prognosis is worse than in osteogenic sarcoma.

Bradley Coley, in a large series of cases, did not have a single 5-year cure.

Treatment. The tumor is radiosensitive; however, radiotherapy will not cure. Perhaps a combination of X-ray therapy and surgery will offer more hope.

Hemangioma of Bone. Hemangioma of bone occurs at all ages and in nearly all bones. It may arise in the periosteum or in the marrow. Extensive angiomas of the skull have been observed. Bucy and Capp state that the tumor is most frequent in the vertebrae and flat bones. In the flat bones, the cavernous angioma produces a characteristic radiographic appearance of a sunburst of radiating opaque striae due to sclerosed bone between the cavernous spaces. In the long bones, hemangioma widens the shaft with a multicystic expansive tumor which generally fails to perforate the periosteum. Fracture is not uncommon. The radiographic appearance varies with the structure but is generally coarsely multicystic, somewhat resembling a giant-cell tumor.

Multiple Myeloma. Multiple myeloma is a clinical and anatomical tumor of bone whose origin is in the myeloid tissue of the marrow.

Etiology. It is commoner in males than in females and usually occurs between 40 and 60 years of age. Occasional cases are seen at the age of 30, and there have been reports of cases in childhood and adolesence.

Frequency. It is almost as common as osteogenic sarcoma and more common than chondrosarcoma and Ewing's tumor.

Anatomy. Every bone may become involved in any given case. The progress of the disease is variable. It may be steady, or it sometimes begins to develop after a latent or static period. In some cases, before becoming widespread throughout the skeleton, it may flourish in one bone (solitary myeloma). Those tumors called arrested are in reality not arrested, but have not been followed over a long enough period of time; the disease may remain latent for as long as 10 years. It is only seldom that the disease shows any spread to the viscera. On rare occasion, one may find tumor masses in the liver, spleen, and lymph nodes.

X-Ray. The clinical description of X-ray changes that one reads in textbooks (multiple punched-out defects in bone generally and especially in the skull and the appearance of Bence-Jones protein in the urine) are found in advanced cases. This picture is the exception rather than the rule. If one relies completely on the picture alone, most cases of myeloma will remain undiagnosed. In the early cases, one sees vaguely defined rarefactions

Ewing's Tumor

Etiology. Specific etiological factor unknown.

Age. Between 10 and 25 years.

Clinical Symptoms. The presenting lesion (that is, the one causing the complaints which lead the patient to seek medical care) is most commonly in a long bone or one of the bones of the trunk—very often an innominate bone.

Clinically, in a given case, persistent mild fever, secondary anemia, and an increased sedimentation rate of the blood can be taken as evidence of an infection. As autopsy discloses, the evolution of the disease is regularly associated with widespread involvement of the skeleton, practically all the bones eventually becoming riddled through with tumor tissue.

Differential Diagnosis. In children, neuroblastoma metastasizing to the skeleton must be considered; in adults, metastatic carcinoma; and between 40 to 60 years of age, multiple myeloma.

X-Ray. The characteristic X-ray picture described as onion peel is not reliable. It is seen only occasionally. The picture is variable and cannot be defined. The lesion is lytic and shows mottled rarefaction, and later penetrates the cortex. One must consider and rule out osteomyelitis, other malignant tumors, and eosinophilic granuloma of bone.

Pathogenesis. Oberling believes that the tumor cells of the Ewing sarcoma are derived from the supporting framework (the reticular tissue) of the bone-marrow—a framework which can be regarded as mesenchymal or primitive form of connective tissue. This idea does not support Ewing's own contention that the tumor cells are derived from capillary or vascular (or perivascular) endothelium.

Histology. In well-preserved tumor tissue, *the cells appear in a sort of network, lack delimiting membranes, are connected by short or long cytoplasmic processes, and have a fairly large, round, or oval nucleus showing scattered chromatin.*

Microscopically, one is dealing essentially with a round-cell tumor which is difficult to differentiate from other round-cell tumors, such as neuroblastoma, metastatic carcinoma, and lymphosarcoma. The tumor must be distinguished from reticulum cell sarcoma, multiple myeloma, fibrosarcoma, hypernephroma, carcinoma of the prostate with metastases, and osteoid osteoma.

Differential Diagnosis

Reticulum cell sarcoma must be distinguished from Ewing's sarcoma. If it starts in a long bone, it may be localized for a year or two.

Multiple myeloma has smaller cells, clearly blocked out and delineated cytoplasm; whereas in Ewing's sarcoma the cells are large, nuclei are pale, and the cytoplasm is not blocked out.

Some *fibrosarcomas* originate from connective tissue of bone but do not form bone. Some may be or neurogenic origin.

Hypernephroma often has a solitary skeletal metastasis and, curiously, it is often in the proximal portion of the humerus.

Carcinoma of the prostate with metastases produces dense metastases and is prone to develop in the spine and pelvis.

absent early in the disease and may become positive as the disease advances. When found, it points strongly to a diagnosis of multiple myeloma. It may occur on rare occasion in such conditions as leukemia and carcinomatosis. For all practical purposes, its presence strongly points to a diagnosis of multiple myeloma, but its absence does not mitigate against it.

Kidney Changes. A certain degree of renal insufficiency arises as a result of formation of protein casts obstructing the tubules. The urine shows casts and often albuminuria and, later in the disease, the nonprotein nitrogen may begin to rise.

Sternal Marrow Puncture. The puncture reveals nests of myeloma cells; however, there are occasional cases which fail to show the nests of myeloma cells in the marrow.

Hematological Findings. More than one-half of the cases show some degree of anemia and, as the disease progresses, the anemia tends to become more severe. Transfusions have only a temporarily sparing effect. Blood smears show many normoblasts, indicating irritation of the marrow. Often the disease is mistaken for myeloid leukemia.

As the disease progresses, constitutional changes appear, consisting of (1) loss of weight and (2) weakness and vague aching pains in the chest and back without any localizing complaints.

Differential Diagnosis. This condition must be differentiated from carcinomatosis of bone, leukemia, hyperparathyroidism, osteoporosis, etc.

Prognosis. The average patient does not survive for more than 2 years. Occasional cases are characterized by spontaneous remissions and several cases have gone on for from 7 to 9 years.

Treatment. At the present time, there is no known cure. X-ray therapy often relieves bone pain. Stilbamidine relieves pain in late cases, but it has toxic side effects and may produce a trigeminal neuralgia.

Summary:

1. *X-ray.* The picture is varied. One often cannot make the diagnosis from X-ray.
2. *Urine.* Bence-Jones protein is present in 50 percent of cases.
3. *Blood chemistry.* Serum calcium increased. Serum globulin increased. Serum albumin decreased.
4. *Renal function.* The nonprotein nitrogen is elevated late in the disease.
5. *Sternal marrow puncture.* Nests of myeloma calls.

Lymphosarcoma in Bone. *Etiology, Unknown.* The *age incidence* does not vary from that found in the general group of patients with lymphosarcoma. Both *sexes* are affected equally, and the patients are usually over 20 years of age.

Involvement of the Bone. The involved bones in order of frequency are: Spine, pelvis, skull, femur, humerus, tibia, scapula, mandible, fibula, and ribs.

X-Ray Studies. The lesions in the bones are either predominantly osteoplastic or osteolytic. In the long bones the disease has no predilection for the part containing marrow but infiltrates the bones extensively. As the disease progresses, the entire bone is frequently involved. A progression

in the ribs, spine, scapulae, and pelvic girdle, or an exuberant tumor focus in a rib or femur. The tumor often presents itself clinically because of its presence in a vertebral body or bodies with resultant compression or even collapse. The complication of collapse and extradural compression by the tumor results in neurological symptoms.

Diagnosis. The disease is frequently missed clinically—perhaps because of the undue reliance placed on the textbook picture and because of the unfamiliarity with the varied manifestations that the disease can produce. It is a good general rule to make a presumptive diagnosis of multiple myeloma whenever one notes a flattened compressed vertebral body in a patient between 40 and 60 years of age without a history of trauma. Metastatic carcinoma, however, can produce the same picture.

Skull Involvement. In about one-third of the cases in a representative series there is skull involvement when other bones show involvement, but this is not invariably so. When other bones fail to show clearcut involvement, the skull will not show changes by X-ray examination. The marrow in the calvarium is often mottled by myeloma cells but, unless there is erosion of the tables, one cannot discern punched-out areas by X-ray examination.

Amyloid. In about 10 percent of the cases of multiple myeloma, amyloidosis is associated with the tumor. It may be present in the tumor tissue, in the bones, and in the viscera as well. Extraskeletally, amyloidosis occurs in atypical sites (in organs ordinarily spared by amyloid, such as the heart, lungs, skin, tongue, muscles, periosteum, and joint capsules). One must think of multiple myeloma as the causative agent in every case of unexplained amyloidosis.

Hypercalcemia. In about one-half of the cases of multiple myeloma, hypercalcemia is observed. As the skeleton becomes demineralized, particularly in the presence of kidney damage, hypercalcemia is observed. When the calcium level rises to its upper limit, there is a strong tendency to metastatic calcification, especially to the kidney. At this stage of the disease, hyperparathyroidism must be considered in the differential diagnosis, and the alkaline phosphatase value is important in distinguishing the two conditions. The alkaline phosphatase value is normal in multiple myeloma unless a recent fracture is present, at which time there might be a slight elevation. In hyperparathyroidism, the alkaline phosphatase level is regularly increased.

Blood Protein Changes. In about one-half of the cases, there is hyperglobulinemia. In multiple myeloma, the globulin may rise from 3 to as high as 14 gm., and the serum albumin tends to be reduced, ranging from 2 to 4 gm. In those cases showing an elevated protein, one may usually find (1) rapid sedimentation rate, (2) autohemoagglutination, (3) abnormal increased viscosity of blood, and (4) rouleaux formation. An increased serum globulin may also occur in other conditions, such as (1) certain infections, (2) lymphogranuloma venereum, (3) kala-azar, (4) cirrhosis of the liver, (5) chronic nephritis, and (6) bacterial endocarditis.

Bence-Jones Proteinuria. The excretion of this protein is intermittent; hence a single urine specimen may fail to show its presence. It may be

onto the outer surface of the body of the bone, producing the cartilage-covered excrescences. The latter, according to Keith, are thus merely the secondary results of the primary disorder of bone growth and especially bone modeling which he denotes in the name "diaphysial aclasis."

Jaffe holds that the theory of defective modeling and that of perverted periosteal and perichondral activity are not only mutually compatible but reenforce each other in explaining the genesis of the disorder as a whole.

Inheritance. Affected males hand on the disorder to about 52 percent of their children and affected or tainted females to about 42 percent.

The offspring of subjects with relatively few exostoses tend to have relatively few, while the offspring of subjects with numerous exostoses tend to have large numbers. However, in any affected family tree the exostoses tend to become more numerous from generation to generation.

Clinical Aspects. In addition to presenting a knobby appearance, the more severely affected subjects may show definite shortness of the limbs in relation to the trunk. Consequently, the superficial appearance may resemble that of mild achondroplasia, but the patients do not present other stigmas of that disease. ***The shortness of the long bones is due in the main, not to direct interference with longitudinal growth at the epiphyseal cartilage plates (as in achondroplasia), but to dissipation of the longitudinal growth force in a lateral direction at the metaphyses.***

Through the supplementary agency of curvature and deformity of the forearm, one or both upper limbs are likely to be even more strikingly shortened than the lower.

Symptoms. Symptoms result from—

(1) Pressure pain.
(2) Hindrance of full normal articular motion.
(3) Disturbances of stance and gait.
(4) Curvature of a long bone.
(5) Discrepancy in leg lengths.
(6) Scoliosis.

Deformity of the forearm occurs in about one-third of any representative series of cases.

In most instances, outgrowths which impinge upon a peripheral nerve, a large blood vessel, or a part of the spinal cord are due to exostoses which may have undergone malignant transformation.

Pathology. In fully developed cases of multiple exostoses, one notes that the involvement is much more extensive than it appeared to be by clinical examination. The exostoses tend to follow a definite pattern of distribution in that they develop particularly (in most instances) in relation to sites of bone growth at the epiphyseal cartilage plates. The lesions tend to be bilateral and symmetrical; however, in exceptional cases, one side of the body may be more severely involved than the other.

The skull bones are usually exempt of lesions. However, occasional pea-sized lesions may be found at the base of the skull, the bones of which are preformed in cartilage. Small pointed or warty cartilage-covered exostoses may be found on the bodies of the ribs, especially at the chondral end and also posteriorly. Scapulae are usually definitely affected. The exostoses

of the disease is found to accentuate further the two varieties of osseous change. In general, the osteolytic changes are seen more frequently.

In the pelvis and skull, many small punched-out areas are seen with occasional surrounding sclerosis.

In the long bones, a diffuse destructive process is common. Infiltration is the rule, often causing partial collapse of the diseased bone with fracture. [illegible] of the cortex associated with a periosteal reaction. The diffuse involvement of the bones with predominant osteolytic changes is characteristic of the disease.

The *microscopic appearance* reveals a diffuse growth of lymphoid cells lying in the reticular tissue. The individual cells vary in size. The general structure of the lymph nodes is obliterated.

Differential Diagnosis. Lymphosarcoma affecting bones may be confused with the metastatic carcinoma, Hodgkin's disease, Ewing's tumor, the leukemias, and osteomyelitis.

Treatment. X-ray therapy may be used as a palliative measure.

Liposarcoma. Primary liposarcoma of bone has been infrequently described in the literature. Ewing, Duffy, Stewart, and Barnard have described the condition in case reports. There are several peculiarities which serve to separate this tumor from spindle cell medullary sarcoma of bone. The origin of this tumor is unknown; however, it is believed by Duffy and Stewart that it is traceable to inflammatory changes in adult fat.

Grossly, the tumor is soft, grayish yellow, and lobulated and has a coarsely fascicular structure.

Microscopically, the appearance is quite characteristic, and one must view serial sections to diagnose the lesions.

B. SYSTEMATIZED ANOMALIES OF SKELETAL DEVELOPMENT

1. Multiple Exostosis. *Etiology.* It is the most comon of the systematized anomalies of skeletal development. Males predominate. The disease rarely manifests itself before 2 years of age. Cases are brought to attention because of (a) *deformity* or (b) *serious complication, such as development of a chondrosarcoma.*

Virchow pointed out that exostoses are derived from bits of cartilage that became snared off from the lateral margins of the plates. This explanation appears to be inadequate.

A perversion of the periosteal activity has also been considered as a likely causative agent.

Keith pointed out the well-established fact that normally at growth zones (epiphyseal cartilage plates and their analogues) a core of bone formed by encochondral ossification becomes encased in a sheath of bone formed by the ring of periosteum surrounding the growth zone. He maintained that the primary basis of the genesis of multiple exostosis is defectiveness of this periosteal ring. *In regard to the disorder in question,* Keith stated that, on account of the deficiency or absence of deposition of bone by the periosteal ring, the cartilage-preformed bone at the growth zone is free to expand in abnormal directions, so that the normal confining and modeling at that zone fails to take place. Thus the new bone formed at the growth zone, not being restrained and subjected to active remodeling, "spills out," as it were,

generation usually manifests itself in adults; however, children and adolescents sometimes show this complication.

It appears that chondrosarcoma may evolve out of the cartilaginous cap of one or another of the exostoses or out of the residuum of this cap. It may conceivably also evolve out of a mere cartilage rest which has been lying between the periosteum and the cortex of the affected area of bone. The tumor may grow rapidly to large size, soon break into regional venous channels, reach the heart and the lungs by intravascular growth, and even give rise to parenchymal metastases, at least in the lungs.

If a microscopic section reveals several or more binuclear cartilage cells or many cartilage cells with plump nuclei, especially with cartilage cells containing large or multiple nuclei, the growth should not be considered benign.

Supposed Interrelations Between Multiple Exostosis and Enchondromatosis. Multiple exostosis and skeletal enchondromatosis should be regarded as clinically and anatomically independent disorders.

Treatment. In general, when exostotic areas are excised, the periosteum should be removed with them and not stripped back.

Indications for Surgery

1. Interference with motion of a joint.
2. Local pain.
3. Cosmetic.

(Radiation for chondrosarcoma has no therapeutic effect on the course of the growth.)

2. Fibrous Dysplasia. This is a condition affecting one, several, or many bones, in the graver cases of which there may be abnormal pigmentation of skin, premature sexual development, hyperthyroidism, or still other extraskeletal abnormalities.

This condition represents an expression of some deeply rooted congenital defect of development. The etiology is unknown. In any representative series of cases, males tend to be less commonly affiicted than females.

Gross. One, several, or many bones may be involved in any particular case of fibrous dysplasia. When more than one bone is affected, the involvement tends to be unilateral or predominantly unilateral. In an affected bone, the area implicated may be rather limited or very extensive. The *contour* of the bone as a whole may still be found normal but is more likely to be found *distended* in all or at least part of the affected area. Even when not expanded, the *cortex* is likely to be found *thinned by erosion from the medullary side.* In the area involved, the *interior of the bone is found to be filled mainly by a rather rubbery and compressible tissue,* which may be more or less uniformly whitish or may show reddish speckling where there is vascular dilatation and congestion and perhaps capillary hemorrhage. *Fundamentally, this is fibrous connective tissue.* It may be gritty throughout from the presence everywhere in it of newly formed trabeculae of immature bone. On the other hand, it may show some smaller or larger nongritty, highly collagenous areas in which few, if any, bony trabeculae are to be found. In some lesions, islands of hyaline cartilage may also be present within the fibrous connective tissue. In an occasional lesion, *focal*

are usually prominent and numerous along the iliac crest. The vertebral column presents only a few exostoses, and these are usually located close to the secondary centers of ossification.

Gross Pathology as Shown in Affected Long Bones. Over a considerable distance away from each epiphyseal end, the shaft is wider and blunter than it would normally be. The surface is knobby and bumpy. The projections tend to curve away from the epiphyseal ends of bones. It is not uncommon to find a thickened bursa overlying a large exostosis. It should be noted that the periosteum of the unaffected part of the shaft continues over the exostotic area. After removal of the periosteum, it is noted that the knobby surface of the affected region is cartilage-capped in some places and osseous in others. The exostotic area is not superimposed on a delimiting cortex, but, instead, the outline of the exostotic area represents irregularly outpouched cortex. In young subjects, it can be noted that the centers of ossification for the epiphyses have apparently been growing normally and that the epiphyses themselves are fairly normal in shape. The chronology of fusion of the epiphyses with the shafts tends to be fairly normal.

Microscopic Pathology of an Exostotic Lesion. The cartilage is hyaline in nature and may be relatively thick and may show on its inner surface considerable growth activity in the form of active endochondral ossification. Where the cartilage is not proliferating, the columnar arrangement of its deeper cells is not apparent and the cartilage rests on a thin plate of bone.

As already noted, the periosteum covering the surface of the affected area is continuous with the periosteum over the unaffected areas. Where it runs over prominent cartilaginous surfaces it appears as a thin, rather poorly cellular, highly collagenous connective tissue layer corresponding to the outer fibrous coat of periosteum in general. In areas not capped by cartilage there is also a relatively thick inner cellular zone which corresponds to the cambium layer of periosteum in general, but this layer is remarkable on account of its thickness. If one searches different microscopic fields, one can find evidence of focal cartilaginous metaplasia occurring in this cellular, cambium-like layer of the periosteum.

One additional point should be noted. Occasionally below the surface in an exostotic area, one sees a smaller or larger focus of gritty calcareous material. Histologically this consists in the main of calcified (largely necrotic) cartilage, calcified acellular cartilage matrix, and calcium detritus. Such a focus probably results from some local disturbance of the normal course of endochondral ossification associated with the growth of the exostotic area, so that calcified cartilage and cartilage matrix which should have been destroyed and replaced by bone have accumulated under the proliferating cartilage. The finding of such a focus should not, however, be regarded as evidence that in the exostotic area in question an enchondroma is present along with the osteocartilaginous exostosis. Indeed such gritty calcified foci originate, not from the interior of the bone, but from the surface of the lesions and are related to the proliferating cartilage on that surface.

Chondrosarcoma as a Complication. The true incidence of this complication is probably greater than is ordinarily suspected. The malignant de-

generation usually manifests itself in adults; however, children and adolescents sometimes show this complication.

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Gross Pathology as Shown in Affected Long Bones. Over a considerable distance away from each epiphyseal end, the shaft is wider and blunter than it would normally be. The surface is knobby and bumpy. The projections tend to curve away from the epiphyseal ends of bones. It is not uncommon to find a thickened bursa overlying a large exostosis. It should be noted that the periosteum of the unaffected part of the shaft continues over the exostotic area. After removal of the periosteum, it is noted that the knobby surface of the affected region is cartilage-capped in some places and osseous in others. The exostotic area is not superimposed on a delimiting cortex, but, instead, the outline of the exostotic area represents irregularly out-pouched cortex. In young subjects, it can be noted that the centers of ossification for the epiphyses have apparently been growing normally and that the epiphyses themselves are fairly normal in shape. The chronology of fusion of the epiphyses with the shafts tends to be fairly normal.

Microscopic Pathology of an Exostotic Lesion. The cartilage is hyaline in nature and may be relatively thick and may show on its inner surface considerable growth activity in the form of active endochondral ossification. Where the cartilage is not proliferating, the columnar arrangement of its deeper cells is not apparent and the cartilage rests on a thin plate of bone.

As already noted, the periosteum covering the surface of the affected area is continuous with the periosteum over the unaffected areas. Where it runs over prominent cartilaginous surfaces it appears as a thin, rather poorly cellular, highly collagenous connective tissue layer corresponding to the outer fibrous coat of periosteum in general. In areas not capped by cartilage there is also a relatively thick inner cellular zone which corresponds to the cambium layer of periosteum in general, but this layer is remarkable on account of its thickness. If one searches different microscopic fields, one *can find evidence of focal cartilaginous metaplasia occurring in this cellular,* cambium-like layer of the periosteum.

One additional point should be noted. Occasionally below the surface in an exostotic area, one sees a smaller or larger focus of gritty calcareous material. Histologically this consists in the main of calcified (largely necrotic) cartilage, calcified acellular cartilage matrix, and calcium detritus. Such a focus probably results from some local disturbance of the normal course of endochondral ossification associated with the growth of the exostotic area, so that calcified cartilage and cartilage matrix which should have been destroyed and replaced by bone have accumulated under the proliferating cartilage. The finding of such a focus should not, however, be regarded as evidence that in the exostotic area in question an enchondroma is present along with the osteocartilaginous exostosis. Indeed such gritty calcified foci originate, not from the interior of the bone, but from the surface of the lesions and are related to the proliferating cartilage on that surface.

Chondrosarcoma as a Complication. The true incidence of this complication is probably greater than is ordinarily suspected. The malignant de-

surface of the cortex, and there is never any evidence of scalloped erosion beneath the periosteum, as seen in hyperparathyroidism.

As to contour, an affected bone may remain normal but often it is more or less expanded instead.

Cases Presenting Moderate Involvement. The distribution of the bone lesions as a whole tends to be exclusively or at least predominantly one-sided. An occasional patient of either sex presenting the moderate form of skeletal involvement will exhibit also one or more yellow-brown pigment patches on the back, buttocks, or elsewhere.

Cases Presenting Severe Involvement. The cases placed in this category are those in which a major, or at least a substantial part of the skeleton is found affected. Bones of two, three, or even all four limbs may be involved, and all combinations of upper and lower limb implication have been observed.

Extraskeletal Aspects of the Disease.

(1) Pigmentation of skin.
(2) Premature sexual maturation.
(3) Hyperthyroidism.
(4) Premature skeletal growth and maturation.
(5) Cardiovascular and other developmental anomalies.

Treatment. A solitary lesion uncovered only incidentally in the course of a routine physical examination can, in many instances, safely be left entirely alone after the diagnosis has once been established, perhaps with the aid of a biopsy. The surgical measures to be considered in the treatment of this condition are curettage and resection of the diseased area. In those cases showing marked skeletal involvement, osteotomies and other corrective procedures may be necessary to obtain good results.

3. Morquio's Disease. *Morquio's disease is primarily a disturbance of the metamorphosis of cartilage into bone and is a dysplasia rather than an aplasia. There is a disturbance of ossification of the epiphyses whereby the epiphysis instead of developing from a single center, develops from multiple anomalous centers of ossification, resulting in a deformed bone end.*

General development is, as a rule, delayed but little. As development proceeds, skeletal deformities occur and advance. One of the most characteristic findings is the appearance of a distinct kyphos of the spine. This is due to a wedge-shaped malformation of one or more of the vertebral bodies occurring characteristically at the thoracolumbar junction. *X-ray examination reveals fragmentation and distortion of the epiphyses.* There is relatively little disturbance of growth in length of the extremity, but there occurs malformation of the joints.

Systems other than the skeletal system are often involved in the disease process.

4. Achondroplasia. *Etiology.* Unknown. The condition is hereditary, but whether the defect is primary in the anlage of the cartilaginous bones or secondary to hereditary or acquired defects in the amnion is controversial.

Clinical Aspects. Patients are short-limbed dwarfs with unimpaired mentality and vigorous musculature and sexual development.

degeneration of this tissue may have led to the formation of *small secondary cysts.*

Microscopic. Specifically, apart from the osseous or the cartilaginous elements it may contain, the connective tissue, in some places or throughout, may be rather cellular, composed of immature, small, slender spindle cells in rather loose and whorled arrangement. The connective tissue in the affected area is likely to present trabeculae of bone formed through metaplasia. The connective tissue as a whole tends to be avascular; however, occasional thin-walled blood channels may be seen. Blood extravasations may surround the channels. Occasional giant cells may be prominent in relation to the blood vessels or blood extravasation. They appear to represent multinuclear skeletal phagocytes. Occasional small islands of hyaline cartilage may be seen in the connective tissue and apparently these islands result from metaplasia.

Cystlike areas which are also occasionally seen are developed secondarily as a result of softening of the connective tissue in the interior of the bone.

X-Ray Findings. The roentgen picture of the solitary lesion may be quite difficult to interpret because of the variation from case to case. These lesions may be mistaken for (1) bone cyst, (2) enchondroma, or (3) giant cell tumor. Thus, for a definite diagnosis, a biopsy is necessary.

Cases Presenting Involvement Limited to Few Bones. In general, what has been said about the roentgen picture presented by the affected bone when only one is involved applies also to the individual affected bones in the polyostotic form of the disorder. Should several bones of a single limb be affected, with or without adjacent trunk bones, the diagnosis of fibrous dysplasia ought to suggest itself promptly, though the possibility of the limited form of skeletal enchondromatosis (Ollier's disease) should also be considered.

An individual bone considerably involved in fibrous dysplasia presents *roentgenographically* a number of *discrete rarefactions,* or, if the latter have become confluent, the major part of the bone may appear more or less diffusely rarefied. The rarefactions reflect the replacement, in the affected area, of the spongy bone and of the adjacent inner surface of the cortex by fibrous connective tissue, which, of course, is relatively radiolucent. If within this tissue there has been substantial metaplastic ossification, the rarefaction shadow is likely to present a mottled or rather cloudy ground glass appearance. The latter expresses the character of the immature new bone. In some lesions one may even note stippling here and there, indicating the presence of islands of ossifying cartilage.

The cortex in the affected area is usually found thinned and it may even have been reduced to a mere shell in consequence of erosion of its endosteal surface by the dysplastic fibrous tissue. However, the latter does not perforate the cortex and extend into the parosteal tissue. Except in the region of a fracture, the outer surface of the thinned cortex shows no periosteal new bone apposition. Any new, reenforcing periosteal bone being laid down is deposited so slowly that roentgenographic evidence of it is generally lacking. On the other hand, there is no appreciable resorption of the outer

surface of the cortex, and there is never any evidence of scalloped erosion beneath the periosteum, as seen in hyperparathyroidism.

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Pathology.—Gross. The shafts of the long bones are short and broad, and the epiphyses are broad and overhanging. The second to fifth digits of the hand are of about equal length. It is highly characteristic that the fibula is longer than the tibia.

Microscopic. There is symmetrical protrusion of connective tissue into the space between the diaphysis and epiphysis.

The centers of ossification of carpals and metacarpals may appear and develop at the normal time and in normal fashion, but in severe cases their appearance may be delayed and their outlines irregular.

5. Enchondromatosis. *The pathological changes occurring in skeletal* enchondromatosis are the same as those that occur in a *solitary enchondroma.* Enchondromatosis is an hereditary anomaly which often has a predilection for one side of the body. The condition is then termed *Ollier's disease.*

6. Cleidocranial Dysostosis. There is a strong hereditary factor in this disease, usually as a Mendelian dominant. The clavicles are incompletely formed, and the bones of the cranium are separated by large fontanels. The jaws are deformed by unerupted teeth. The facial skeleton is abnormal.

7. Osteogenesis Imperfecta. *Classification.* The hereditary type, which is called an hereditary hypoplasia of the mesenchyme with brittle bones and blue sclera and the nonhereditary congenital type which consists of two groups: (*a*) Osteogensis imperfecta congenita and (*b*) osteogenesis imperfecta tarda. A blue sclera is considered requisite for the first group, whereas it may or may not be present in the second group.

Etiologic Factors. The etiology is unknown. However, the fault lies in some inherent defect in the germ plasm, which does not allow the mesenchymal tissue to develop normally.

Fractures. In any series of cases examined, it will be noted that multiple fractures occur in all the cases. Pain associated with these fractures is usually less than normal. The incidence of fractures decreases sharply after adolescence.

Laboratory Findings. Routine examination of blood, urine, calcium, and alkaline phosphatase reveals values within normal limits.

Pathology. The pathological picture is characterized by bone which is deficient in quantity and poor in quality.

Treatment. There is no known specific therapy for this condition.

8. Marble Bones (Albers-Schönberg Disease: osteopetrosis). Marble bone disease is due to the influence of an unknown agent which damages the bone-forming blastema at the beginning of the second period of the development of each individual bone. From this time on, the differentiation of bone tissue is retarded and the less differentiated types become hyperplastic. The malformation is responsible for the general retardation of resorption, because the two phases of the bone-forming process—deposition and resorption—condition and stimulate each other. In marble bone disease the threshold of response to stimuli which bring about resorption is raised. Resorption is arrested at the beginning of the second period for a long time. The results are fetal size and shape of the marrow cavity, a thick cortex composed of all the embryonic strata which normally are removed, and an unusual amount of spongiosa. The clubbing of the ends of long bones

is the result of the hyperplasia and persistence of less differentiated types of bone tissue in the metaphyses. The greater density of marble bones in the roentgenogram is due partly to a greater density of structure when the bones are in a state of repair (eburnation) and partly to a higher calcium content, revealed indirectly by the scarcity of fibrils in all the types of bone tissue involved. The anemia in marble bone disease may be due to the same agent which impairs the differentiation of bone tissue. It is more likely that it is due to the relative lack of a substance which normally is released by the resorption of bone and stimulates the hemopoiesis.

9. Osteopoikilosis (Spotty Bones). *Etiology.* The condition is hereditary.

Pathology. The dense bodies seen on X-ray are simply compact bone in abnormal situations. Cases of multiple involvement are uncommon.

Clinical Features. No symptoms are produced by this condition. This is an anomalous condition of the bones marked by the presence of large numbers of small dense bone islands in otherwise normal cancellous bone. It affects particularly the bones of the extremities, but it may involve the short and flat bones.

C. SKELETAL CHANGES PRODUCED BY VITAMIN DEFICIENCY

1. Vitamin A. Wolbach has shown experimentally that vitamin A is essential for the normal activities of epiphyseal cartilage cells. Vitamin A deficiency suppresses epiphyseal cell sequences; remodeling sequences fail to occur. Excessive vitamin A administration accelerates those growth sequences of bone retarded by the deficiency; it causes rapid consumption of epiphyseal cartilage.

2. Vitamin C. Scurvy (the infantile form is also known as Barlow's disease) is the chief clinical manifestation of C avitaminosis.

Etiology. Lack of vitamin C.

X-Ray. a. A fairly irregular, broadened, well-calcified epiphyseal line. The term "epiphyseal line" is used to designate the gap between the calcified portions of diaphysis and epiphysis.

b. A small spur on the lateral edge of the epiphyseal line or occasionally dislocation of the entire epiphysis.

c. An area of decreased density, "the scurvy line," immediately back of the epiphyseal line, representing lack of calcification of the newly formed spongiosa.

d. A very thin diaphyseal cortex, often merely a narrow white line.

e. Glasslike transparency of the shaft; no coarse trabeculation of the sort seen in rickets or some normal bones.

f. A broad, rather irregular, white edge on the epiphyseal center of ossification of the long bones.

g. Elevated periosteum due to subperiosteal hemorrhages.

Pathology. The bone-marrow loses its blood-forming elements and becomes converted into an edematous fibrous tissue in which the blood vessels and osteoblastic cells seem relatively few. As a result, bone formation becomes almost stagnant everywhere, and, since the resorption of bone goes on normally, the whole structure shortly becomes rarefied. At the epiphys-

eal line the lack of proper and orderly invasion of the cartilage columns is very marked. As shown clearly in the studies of Park and his co-workers, there remains a layer of calcified bands of matrix, very fragile and susceptible to fracture, which he calls the lattice. Sometimes there is irregular or oblique invasion, and the zone of osteogenesis becomes broadened where there is a network of capillaries, but this is also an ineffectual method of bone formation. Usually only scattered laminae are produced, and in some cases a sort of bony wall is formed transversely which obstructs further ossification. Hemorrhages occur as elsewhere in the body, in the joints, underneath the periosteum, and in the substance of bone-marrow. The periosteum may be elevated from a large part of the shaft of the bone by the effusion of blood. Periosteal growth of bone tends to replace the clot, but the cortex continues to be rarefied. The disturbances of ossification do not depend on the hemorrhages, since they precede them.

Treatment. Massive doses of vitamin C.

3. Vitamin D. Rickets begins at *6 months of age* and may last for several years with remissions and healing, if untreated. After healing, it is remarkable how normal some of the bones may appear. In occasional cases of florid rickets, the deformities may persist in spite of healing.

X-Ray Findings. In untreated rickets, the characteristic findings consist of:

a. Absence of ossification centers within the epiphyseal cartilages.

b. Metaphyseal plates of the femur and tibia irregularly broad and ill-defined.

c. Wide transparent space separating the visible ends of the femur and tibia.

d. The ends of the shaft tending to flare.

e. The shafts less dense than normal.

Pathology. The zones of provisional calcification and primary spongiosa, which together make up the metaphyseal plate and are normally thin and sharply defined, suffer gross disorganization in rickets. New calcification of cartilage matrix ceases and old calcium disappears, while ossification of new spongiosa becomes irregular, and incomplete, and then ceases altogether. Bone growth is not arrested; hence the shaft continues to elongate, but the newly formed portion, being made up of cartilage islands, blood vessels, and noncalcified osteoid tissue, is not visible in roentgenograms. The tissue of this transparent, defective shaft end is bulkier than normal bone and can be felt on physical examination as a knoblike swelling in the region of the joint. For the most part, it remains uncalcified and, therefore, invisible, but at the junction with the older portion of the shaft some calcification does gradually occur. The part thus visualized by the deposition of [illegible]

In the patients with rickets in whom walking has been initiated, cupping of the diaphyses may be seen roentgenologically. This is supposedly due to mechanical compression.

Osteomalacia is an adult type of rickets, rarely seen in this country. The serum calcium and serum phosphorus values are low and are associated with a high alkaline phosphatase level.

Fanconi syndrome, or *hypophosphatemic rickets,* is a type of low phosphorus rickets, and the condition in general is resistant to vitamin D. The *etiology* is unknown; however, its basis is supposed to be some anomaly of renal function in which there is an excessive excretion of phosphate. These children may show stunting of growth, softening of the bones, widened growth zones, multiple fractures, and scoliosis. (See section on "Metabolic Factors in Bone Growth.")

D. SKELETAL CHANGES PRODUCED BY ENDOCRINES

Skeletal changes arise from:

a. A disturbance in skeletal growth.

b. A disturbance of calcium and phosphorus metabolism.

The endocrine glands which produce skeletal changes are: *Pituitary, thyroid, gonads, parathyroids, pancreas, pineal, and thymus.*

1. Pituitary. The basophilic adenoma of the pituitary produces, from an orthopedic viewpoint, *osteoporosis, round shoulders, tendency to fractures,* and *tendency to backache.* The condition is also associated with obesity, hirsutism, hypertension, gonadal hypofunction, glycosuria, hypoglycemia, and skin atrophy.

Eosinophilic hyperfunction *before puberty* produces a stimulation of endochondral growth with resultant *giantism,* but *after puberty,* the same hyperfunction results in *acromegaly.*

Hypopituitarism. In the *child,* this condition produces *stunting of growth* and delayed sexual maturity.

2. Gonads. *Hypogonadism.* The skeletal changes consist of *activity of the epip*[illegible]

3. Thyr[illegible] *oporosis.*

4. Parc[illegible] disease)

(1) Primary and secondary.

(2) X-ray.

(3) Differential diagnosis.

(4) Pathology.

  (a) Gross.

  (b) Microscopic.

Primary and Secondary (Renal) Hyperparathyroidism. Cases of hyperparathyroidism fall into two categories: *Primary* (or idiopathic) and *secondary.*

The *primary* cases are those in which the *point of origin of the disease is apparently in the parathyroid glands themselves,* since there is no known explanation of what instigates their hyperfunctioning. The parathyroid abnormality in cases of primary hyperparathyroidism may be of the nature of a *tumorous growth* (an adenoma) usually limited to a single gland, or it may be of the nature of a hyperplasia affecting all (i. e., the theoretical four) parathyroids. *In cases of secondary hyperparathyroidism, the point of origin of the disease is elsewhere than in the parathyroid glands themselves.*

Actually, it seems to be exclusively in connection with renal insufficiency of long standing that one may observe a pronounced secondary hyperplasia of all the parathyroids, resulting in a complicating or secondary clinical hyperparathyroidism. *The division into primary and secondary hyperparathyroidism is made on the basis of absence or presence, respectively, of some plausible instigating factor for the parathyroid hyperfunctioning.*

Hyperparathyroidism in its full efforescence has three central facets: *Parathyroid; renal;* and *skeletal alterations.* That is true whether the case being dealt with is one of primary or one of secondary hyperparathyroidism.

X-Ray. The skeletal alterations observable roentgenographically vary widely in accordance with the stage of evolution of the disease. When the *skeletal changes are mild,* one may find merely that the *cortices* of the bones are *rarefied,* even without being thinned, and that their *spongiosa* appears *somewhat obscured.* In other cases, one may note also the presence of slight *subperiosteal scalloping* of the cortices of some of the long bones. The *laminal dura* shows osteoporosis. In such cases, the diagnosis of hyperparathyroidism must rest in abeyance until it has been confined by the clinical and laboratory findings.

An unequivocal X-ray diagnosis of hyperparathyroidism can safely be made only when the lesions in the bones are *fairly advanced.* In such cases, the *cortices* of the bones are *thinned* and the *spongy bone ends* show *blurring of the trabecular outlines.* Also, the *circumference* of some bones may be *expanded* in places by the presence of *cysts and "brown tumors."* In addition, there may be *infractions* and *fractures.*

In the rare cases in which the disease is found well-developed in older children or adolescents, the bone changes visible roentgenographically may suggest those of *adolescent rickets.* In such cases, the *long tubular bones* in particular may show *bowing, widening of the metaphyses,* and *slipping of certain epiphyses.* In advanced cases of hyperparathyroidism, a peculiar granular *mottling of the calvarium* is very likely to be found.

Differential Diagnosis. One must include in the differential diagnosis such conditions as: *Adolescent rickets and osteomalacia, idiopathic steatorrhea, senile osteoporosis, cancer extensively metastatic to the skeleton, multiple myeloma, Paget's disease, and fibrous dysplasia of bone.*

Adolescent Rickets, Osteomalacia, Idiopathic Steatorrhea. In the United States, adolescent rickets is not common at present, and genuine osteomalacia of adults is really rare. Aside from what is revealed by the history, *serum calcium* determinations aid in the diagnosis. In both adolescent rickets and osteomalacia, as contrasted with hyperparathyroidism, the *serum calcium level is at or below the normal.*

Senile Osteoporosis. Occasionally, senile osteoporosis is mistaken for hyperparathyroidism, but in the former condition the *serum calcium, phosphorus, and phosphatase activity values are normal,* unless there are fractures. In the presence of the latter, the phosphatase activity value may be found elevated but not, of course, the serum calcium value.

Carcinosis of the Skeleton. Cancer extensively metastatic to the skeleton sometimes also raises the problem of differential diagnosis. The diagnostic difficulty is most likely to appear if, as happens in rare extreme cases, the

metastatic bone involvement is associated with a hypercalcemia. In any event, even if the primary growth is not clinically evident, there is *one roentgenographic feature which can prevent the diagnosis error. This is the fact that in cancer, no matter how extensive the rarefaction of certain bones may be, or how strongly their appearance may suggest Recklinghausen's disease, other bones, and sometimes even parts of badly affected bones, will be found relatively normal roentgenographically.* In Recklinghausen's disease, on the other hand, when some bones are badly affected all the rest will be found at least somewhat altered.

Multiple Myeloma. Not infrequently, cases of multiple myeloma are misinterpreted as instances of hyperparathyroidism. It is the relatively common finding of a *hypercalcemia* in multiple myeloma that is at the bottom of this confusion. However, in the presence of this finding, further investigation of the blood may reveal a *hyperproteinemia* with an *inversion of the albumin-globulin ratio.* These two findings should be immediately recognized as the cue to the presence of multiple myeloma. Furthermore, multiple myeloma is characterized by the fact that the *serum phosphatase activity tends* to remain *normal,* no matter how extensive the skeletal involvement may be. In addition, it is well known that a good percentage of cases of multiple myeloma also show, sooner or later, a *Bence-Jones proteinuria.*

Paget's Disease. In uncomplicated cases of Paget's disease, the *serum calcium values are normal.*

Fibrous Dysplasia of Bone. It is because roentgenographically the *affected bones appear widened, show thinned cortices, and often present appearances suggesting the presence of cysts* that these cases are so often misinterpreted as instances of hyperparathyroidism. The fact that the *lesions are unilateral or mainly unilateral* and that the *unaffected bones are normal should be enough* to exclude hyperparathyroidism. Furthermore, the *serum calcium and phosphorus values* are normal.

Pathology—Gross. Excessive parathyroid excretion leads to absorption of bone and replacement by fibrous tissue resulting in cystic softening of bone. This condition is associated with a generalized osteoporosis. This gradually increases so that the weight-bearing bones become curved. The bone cysts are usually confined to the bone, but in some cases they make external swellings. Pathologic fractures occur at the site of the cysts.

Microscopic Examination. Microscopic examination of the "cyst" reveals it to be filled with fibrous tissue with occasional interspersed giant cells and hemosiderin deposits.

Hypoparathyroidism. "Chronic idiopathic hypoparathyroidism" is a disease identical with postoperative hypoparathyroidism except that the agent which has interfered with the parathyroid function has not been established. The disease usually starts in childhood or adolescence and, if not then, not until about 40. In several instances the onset has been closely related to acute infections. The serum calcium level should be low, but a more important point is that the serum inorganic phosphorus level should be increased. Renal insufficiency should be ruled out as a cause of the hyperphosphatemia. The bones should be normal by roentgenograms, in order

to rule out rickets or osteomalacia as the cause of the hypocalcemia. The signs and symptoms of tetany should be present. Cataracts and trophic changes of the nails may be present but are not specific for idiopathic hypoparathyroidism.

Tetany is encountered in a number of diseases in no way related to underfunction of the parathyroid glands. These diseases may be divided into two groups: *Those with a low serum calcium level and those with alkalosis. Diseases other than hypoparathyroidism responsible for a low serum calcium level are rickets, osteomalacia, steatorrhea (including sprue), chronic diarrhea, and chronic renal insufficiency. Alkalosis with resulting tetany is seen in hyperventilation, persistent vomiting, following the administration of certain drugs.*

E. ARTHRITIDES

1. Classification. The great majority of the cases of arthritis fall into one or another of five groups:

a. The frankly infectious cases caused by a specific microorganism;

b. Cases that are probably infectious but of unproved etiology;

c. The degenerative forms of joint disease, which in Europe are often spoken of as arthroses;

d. Arthritis resulting from physical injury to the joint by trauma; and

e. Gouty arthritis.

These are the five common divisions of arthritis, and under these main groups there are certain subdivisions. In addition to these five prevalent varieties, however, there are certain rare forms of arthritis, such as the tabetic joint and intermittent hydrarthrosis, which should be included.

a. Infectious Arthritis of Proved Etiology. This general heading includes all cases of arthritis due to infection in which the specific microbic cause can be proved.

The micro-organisms most commonly responsible are the pyogenic cocci, the tubercle bacillus and Treponema pallidum, but many others may occasionally act at the cause of articular infection. Of the pyogenic cocci, the hemolytic streptococcus, pneumococcus, and staphylococcus usually cause a frankly suppurative arthritis which occurs during the course of septicemia or some other severe systemic infection caused by the same agent.

b. Probably Infectious Arthritis, Etiology Unknown. Two of the main divisions of arthritis come under this heading: *The arthritis of rheumatic fever and rheumatoid arthritis.* Under rheumatoid arthritis one may include such clinical variants as *Still's disease* and the ankylosing arthritis, or *Marie-Strümpell disease.*

Rheumatic fever is classified as a disease of unknown origin.

Rheumatoid arthritis is probably a chronic infectious disease, but the specific agent has not yet been determined.

c. Degenerative Joint Disease or Oosteo-Arthritis. Osteo-arthritis represents a degenerative process which involves both the cartilage and the adjacent bone and is entirely different from the arthritis which results from actual infection of the joint. Some authors speak of degenerative arthritis as an arthrosis, and the impression is quite general that the changes which occur in the cartilage and bone often result from prolonged or oft-

repeated trauma. Osteo-arthritis may appear in a generalized or localized form. The disease is much commoner in middle-aged or elderly persons, though occasionally it is encountered (particularly in women) in the thirties.

d. Arthritis Resulting From Physical Injury to the Joint by Trauma. Injury may occur to the synovial membrane, the cartilage, or any one of the ligaments. The ordinary sprained ankle is a good example of the trauma which can lead to this form of arthritis.

e. The Arthritis of Gout. Gout is a disease of unknown origin, though it is commonly defined as a disturbance of purine metabolism.

Other Disturbances of Joints:

(1) *Disturbances of the joints secondary to abnormal postural strain.*
(2) *Disturbances of the joints secondary to lesions of bone.*
(3) Primary neoplasms of the joints (e. g. cyst; hemangioma; synovioma, etc.).
(4) *Disturbances of the joints associated with loose bodies.* Loose bodies can develop in a number of ways:
  (*a*) *From osteochondritis dissecans.*
  (*b*) *Intra-articular fracture fragments.*
  (*c*) *Broken off marginal exostoses in osteo-arthritis.*
  (d) *Synovial osteochondromatosis.*
  (*e*) *Organized fibrin rich bodies from pinched-off synovium.*

In general, joint bodies can derive sufficient nourishment from joint fluid to grow and produce lamellated concretions.

(5) *Disturbances of the joints secondary to functional or psychogenic causes.*

ESSENTIAL FEATURES OF RHEUMATOID ARTHRITIS AND OSTEO-ARTHRITIS

	Rheumatoid arthritis	*Osteo-arthritis*
	Atrophic arthritis Proliferative arthritis Chronic infectious arthritis	Hypertrophic arthritis Degenerative arthritis Menopausal arthritis Senile arthritis
	Clinical Differentiation	
Geographic distribution.	Commonest in temperate climates; rare in the tropics.	Climate not a factor.
Family history	Often a history of rheumatic fever or rheumatoid arthritis in an immediate member of family.	Frequently a history of a similar form of arthritis in one or both parents.
Past history	Occasionally a history of rheumatic fever; frequently of tonsillitis or sinusitis.	Not characteristic; sometimes a history of trauma or faulty body mechanics.
Age at onset	Any age; over 80 percent between 20 and 50.	Rare before 40.
Mode of onset	Rarely acute; usually subacute or insidious; often accompanied by migratory pains.	Insidious; not accompanied by migratory pains.

Clinical Differentiation—Continued

Patient's general condition.	Usually undernourished, anemic, and "chronically ill"; frequently slight fever (99° F.) and slight leukocytosis.	Well-nourished, frequently obese; not anemic. No fever, no leukocytosis.
Involvement of joints.	Symmetrical and generalized; *proximal* interphalangeal joints especially involved.	*Usually* weight-bearing joints, spine, hips, knees; distal joints of fingers (Heberden's nodes).
Appearance of joints.	Early: Periartericular swelling, fusiform fingers. Late: Ankylosis, extreme deformity, ulnar deflection.	Early: Slight articular enlargement. Late: More pronounced articular enlargement; limitation of motion usually slight; never ankylosis; Heberden's nodes.
Muscular atrophy....	Often pronounced, particularly in later stages	Not characteristic.
Cutaneous changes..	(1) Extremities frequently cold and clammy; skin atrophic and glossy; redness of thenar and hypothenar eminences. (2) Psoriasis occasionally present.	No characteristic features.
Subcutaneous nodules.	Present in 15 to 20 percent of cases.	Not present.

Laboratory Differentiation

Agglutination reaction with hemolytic streptococci.	Positive in about 50 percent of typical cases.	Never definitely positive.
Sedimentation rate..	Usually greatly increased; tends to return to normal as patient improves.	Normal or only slightly increased.
Roentgenologic appearances.	Early: osteoporosis, periarticular swelling and joint effusion. Late: Narrowing of joint space, bone destruction, ankylosis and deformities.	Early: No osteoporosis; slight lipping at joint margins. Late: Marked lipping, osteophytes, narrowing of joint space, deformation of articular bone ends.

X-Ray. Differential Diagnosis Between Suppurative Arthritis and Tuberculosis.

In acute suppurative arthritis one finds acute osteoporosis, early decrease in the joint width, bone destruction first on the weight-bearing portions of the articular surfaces, usually little atrophy of adjacent muscles, and a distinct tendency to repair and ankylosis after the early destructive stage. In tuberculosis one finds less osteoporosis, late persistence of the joint width, bone destruction first peripherally on the non-weight-bearing portions of the articular surfaces, usually considerable muscle atrophy, and little tendency toward repair and ankylosis.

In hips, the criteria established by Phemister are not met as readily as in more distal joints.

2. Tuberculosis of Joints. When the skeleton is involved in tuberculosis, the process is most frequently located about the articulations, although in rare instances bone may be primarily affected at points remote from the joints. At the time of pathologic or roentgenologic examination, it is often difficult to state whether the lesion is primarily osseous or primarily articular in origin. This makes it necessary to consider tuberculosis of bones and joints in intimate relationship. Less than 50 cases of tuberculosis of long bones (primary) had been reported by 1946.

Tuberculous arthritis is relatively *more frequent in children* than in adults, and the pathological and roentgenological pictures are somewhat different in the two groups. In young children, the larger joints, in particular the knee, have relatively thick articular cartilages. *Destruction of the non-contacted portions of the cartilages by surface granulations is less complete than it is in adults.* Also, *subchondral granulations do not occur so early* in the disease *or so completely destroy bony articular cortex* and detached articular cartilage. As a result, the *roentgenogram in early tuberculous arthritis in young children may fail to show the characteristic changes.* In the *smaller joints* with thinner cartilages and in older children, *the course is more nearly like that in adults.*

Tuberculous arthritis in adults is *primary* either in the *epiphysis* or in the *synovia.* At the time of roentgenological or pathological examination, it is usually *difficult to tell where the primary focus is located.* The changes in the joint consist in the *formation of tuberculous granulation tissue in the synovia.* This overgrows the surface of the articular cartilage in the regions where it is *not in contact with opposing articular cartilage,* and it produces *surface erosion of the overgrown cartilage, which progresses gradually until the cartilage may be destroyed in its entire extent. Granulations are kept off the cartilage in the region of contact, where it is preserved longest. Subchondral granulations* of a nonspecific nature are formed and gradually absorb the bony articular surface, thereby *loosening the cartilage.* The *cartilage and cortex in the regions of contact may eventually* be *destroyed* and the bone secondarily invaded by the tuberculous process.

When the *primary focus* is in the *epiphysis,* it is *frequently wedge-shaped and the bone is killed,* but it does not break down. Following atrophy of disuse, the *necrotic focus* may be seen as a *wedge-shaped area of greater density than the surrounding atrophied living bone.* It generally *separates as a sequestrum,* and its articular cortex is preserved. In roentgenograms this stands out as a dense line, whereas the lines of the rest of the articular cortex of the joint are lost. When in advance tuberculous arthritis the disease spreads to the bone, it usually *involves both sides at the point of greatest contact* and *pressure in the joint.* This results in the formation of extensive areas of necrosis which gradually become separated from the surrounding bone, with the production of the picture of *kissing sequestra.* Such areas may be recognized in roentgenograms by their *greater density, their rough, cone-shaped appearance,* and *frequently by the preservation* of the shadow of articular cortex, *whereas that of the surrounding and still*

further atrophied, living bone is lost. Secondary sequestra are much more frequently encountered than are primary ones.

F. DISORDERS OF LIPOID METABOLISM

1. Niemann-Pick Disease. One of the diseases of lipoid metabolism of *unknown etiology.* It is thought by some that the disease may have its basis in enzyme defects. The disease tends to run in families. The condition *occurs in infants* during the *first year* and is *usually fatal* by 2 years of age. Patients have an *enlarged spleen and liver,* and one notes an *excess of cholesterol and cholesterol esters in the body.*

2. Tay-Sachs Disease—amaurotic familial idiocy. This is a condition affecting infants at *birth, racial in tendency,* characterized by a *cherry-red spot in the macula* and associated with *abnormal deposition* of *lipids* and *phosphatids* throughout the body.

3. Gaucher's Disease. In Gaucher's disease, a *considerable swelling of spleen and liver* occurs owing to the *proliferation of large cells with a folded and wrinkled protoplasm and a small, round nucleus.* These *Gaucher's cells* are reticulum cells and histiocytes, full of a special nitrogen-containing lipoid, called *kersain.* This substance cannot be visualized by lipoid stains.

The bone-marrow of these patients also contains large amounts of these Gaucher's cells. For this reason the *sternal marrow puncture* has become one of the most important *diagnostic* methods in this disease. At the same time the changes of the spongy bone and of the cortex, under the influence of the Gaucher cell infiltration of the bone marrow, result in typical *bone lesions.* These occur especially in the form of a *bottle-shaped conical swelling of the lower end of the femoral shaft with changes of the structure of the bone and erosion of the cortex.* Lesions of other parts of the skeleton are not infrequent in Gaucher's disease; especially *deformation of the head of the femur* and of the *head of the humerus* with areas of decalcification in different long bones must be mentioned. Vertebral changes resulting in compression fractures of the spine have also been observed.

4. Xanthoma Tuberosum Multiplex. This condition is the *true cholesterol analogue of Niemann-Pick disease.* It is a *familial disease* characterized by a *marked increase* of the *blood cholesterol* (300 to 600 mg.). There is a tendency to deposition of cholesterol in the skin, subcutaneous tissues, tendons, sometimes in the coronaries and occasionally in the bone (spine).

G. DISORDERS OF PURINE METABOLISM

Gout

Etiology. The *etiology* is *not definitely known;* however, it is known that in most cases of gout there is *abnormality in the metabolism of nucleoprotein.*

X-ray findings may be absent in mild or early cases, and, even in advanced cases, where X-rays show bone changes, the appearance is not pathognomonic.

Skeletal tophi are most frequently seen in the *joints of the fingers and toes.* They appear first as *notches* at the *margins of articular surfaces* but in more advances cases *may involve the center of the shaft.*

Tophi situated close to bone erode their way into it, or *urates* are *deposited in subchondral bone*. The *skeletal* tophi thus formed show roentgenologically as rounded defects in the dense trabecular pattern.

Pathology. Apparently as a result of a slight increase of uric acid in the blood, *crystals of monosodium urate are deposited throughout the body in poorly vascularized tissue, such as the cartilage of joints,* the *trachea, and the ear,* and *in tendons and bursae.* These deposits, called "tophi," range in size from small, barely detectable nodules to masses several inches in diameter. When located superficially, the skin above the tophus is apt to be stretched and transparent, so that the chalky nature of the deposits can be seen; this finding is one of the most dependable diagnostic points.

Microscopic sections through tophi show characteristic bundles of *needle-like crystals* which turn purple when treated with nitric acid followed by ammonium hydroxide (*murexide, or Weidel's test*). Most workers agree that urate deposition is the primary affair, not a reaction to injury, and that such reaction as may be noted in surrounding cartilage or bone is a secondary phenomenon.

Treatment

(1) *Low purine diet.*
(2) *Colchicine.*

H. DISEASES OF SYNOVIA, TENDON SHEATHS, AND BURSAE

1. Hemangioma. *Clinical Findings.* Patients have a history of *recurring attacks of pain, swelling, and limitation of motion.* The characteristic recurrent attacks are marked by an elastic, doughy *swelling* of the involved joint which *disappears on elevation of the extremity. Aspiration* of the involved joint reveals the presence of *bloody fluid.* The swelling of the joint is *intermittent* and is usually of *many years' duration,* often dates back to childhood, and is confined to a single joint.

Pathology—Gross. Two gross types are recognized: (1) *A diffuse form limited to the synovial membrane* and (2) *an extensive cavernous form with invasion of the adjacent fascia and muscles.* It is *rare,* indeed, for evidence of *malignancy* to be present.

Microscopic. The microscopic picture reveals large, irregular blood vessels contained in a stroma of loose connective tissue.

Differential Diagnosis. Conditions which must be considered and ruled out are: Hemophilic arthritis; chronic pyogenic infection; tuberculosis; pigmented villonodular synovitis; and syphilitic infections.

Treatment. Excision by *synovectomy* appears to be the most satisfactory treatment. *X-ray therapy* and radium have been used for treatment, and occasional good results have been reported.

2. Pigmented Villonodular Synovitis, Bursitis, and Tenosynovitis. *Eitology.* The condition represents an *inflammatory response,* although the responsible agent is not yet known.

Clinical Aspects—Diffuse Form. The patients who show the diffuse form tend to be *young adults.* The lesion is *more common in males* than in females. Patients' complaints are usually limited to the involved joint and consists of pain and swelling in the affected joint. Trauma does not appear to bear any relation to the condition.

Laboratory Findings. X-ray examination of the involved part does not reveal any evidence of bone involvement but does reveal the presence of *soft tissue swelling.* Determination of the blood cholesterol and cholesterol ester reveals normal values. *Aspiration* of the involved joint reveals the presence of *serosanguineous fluid.*

Circumscribed Form. The lesion tends to occur in an *older age group* than in the diffuse form. The physical findings are similar to those of the diffuse form; however, they are not so prominent.

Gross Pathology. The lesion presents itself in either one of two gross forms—circumscribed and *diffuse.* In the circumscribed form, the affected membrane shows one or more yellow-brown sessile or stalked tumor-like nodular outgrowths. In the diffuse form, the membrane appears brownishly pigmented and covered by villous and coarse nodular outgrowths, though either villi or nodules may predominate in a given case. The tumor appears to have a *predilection for the knee joint,* although the angle joint and other smaller joints may occasionally be involved.

Microscopic. Microscopically, in a synovial membrane showing mainly simple nodular involvement, the more strictly villous portions have essentially the same appearance as the diffusely villous synovial membrane. Whether small or large, sessile or stalked, the nodules present *essentially one cytologic pattern. They are lined by one or more layers of more or less pigmented synovial lining cells. The substance of the nodules is composed of compacted masses of large, roundish or polyhedral cells, a number of which in the more cellular areas show mitotic figures.* There may be a few or even a fair number of multinuclear giant cells. The nodules are only moderately vascularized. Near the periphery, many of the roundish or polyhedral cells may be packed with granules of brown pigment. There may be scattered clumps of foam cells or lipoid-bearing cells in the nodules. Most of the nodules show some hyalinization of the stroma.

The synovial, tenosynovial, and bursal lesions alike are characterized by a strategic polyhedral stromal cellular arrangement found scattered throughout in the villi and nodules. These stromal cells are potential phagocytes, and, soon after they make their appearance, many of them contain granules of hemosiderin.

Pigmented Villonodular Bursitis. The gross and microscopic findings are the same as those just described.

Pigmented Villonodular Tenosynovitis. The lesion tends to occur in almost all instances between the wrist and the fingertips and between the ankle and the toe tips, there being a great tendency for the fingers to be involved. The lesions are usually single in each tendon sheath, although many digits may be involved. The flexor sheath is oftener involved than the extensor sheath. The condition has a predilection for females, and again young or middle age adults are affected. The complaints are those

[illegible]

[illegible] e as those just described. The

[illegible]

Treatment. Surgical excision is the treatment of choice, and, if the lesion is removed in its entirety, recurrences are rare. *Recurrences respond*

sidered are: (1) *The role of trauma;* (2) *the influence of chronic bursitis or chronic synovitis;* (3) *age incidence;* and (4) *sex incidence.*

Trauma. It seems most likely that trauma occasionally initiates the onset of symptoms but by no means produces the tumor.

Chronic Bursitis or Synovitis. A previous bursitis may occasionally predispose to the development of a synovial sarcoma.

Age at Onset of Symptoms. The age incidence is predominantly between the twentieth and fiftieth year, with the average at 34 years.

Sex. Synovial sarcoma occurs more frequently in the male sex.

Clinical Findings

Pain
Tumor
Dysfunction
Swelling

Duration of symptoms. Clinically, synovial sarcomas in knee joints extend over a *long insidious preoperative course covering an average period of several years.* The surgeon, therefore, has a reasonably long period in which to institute radical therapeutic procedures and must be ever on the alert for atypical forms of so-called synovitis.

Location. Approximately one-half of the cases occur in or about the *knee joint.*

X-Ray. Near a joint, and sometimes involving the joint, is seen a *rounded, sometimes rather lobulated, sharply defined soft tissue tumor mass.* No differential diagnosis can be made on such a mass in itself; but when in the mass is found a *scattered and irregular deposit of lime,* a provisional diagnosis of synovioma can be made. This apparent pathognomonic X-ray appearance occurs in about *25 percent* in any representative series of cases.

Gross Pathology. Synovial sarcomas originate in synovial tissue and thus are found in joints, para-articular bursae, and in tendon sheaths. In general they occur in or near a joint, and, since the relationships of the different synovial tissues are extremely variable and complex, it is often difficult in an individual case to establish the exact site of origin.

Anatomically the tumors fall into three groups: Encapsulated, circumscribed, and *diffuse.*

The gross appearance of the tumor is subject to considerable variation. It may be solid, fibrous, and homogeneous, essentially like an encapsulated fibrosarcoma. In general, however, it appears soft, and myxomatous at least in areas. Grossly cystic areas and clefts are occasionally recognized. Yellow-brown pigmentation of the tumor with hemosiderin is sometimes observed. Focal areas of calcification, chondrification, and ossification are found more frequently than in other soft-tissue sarcomas.

Microscopic. The microscopic appearance of synovial sarcoma is variable, and one may note forms ranging from simple malignancy to highly characteristic patterns of growth.

Bennett states that *three basic patterns exist* and are developed with varying degrees of clarity. *One pattern* is represented by the formation of

tissue spaces which vary from slitlike clefts to well-defined glandlike spaces containing serous or mucinous fluid. The *second major design* is the formation of cell tufts. This feature varies from compact groups of oval or polygonal cells segregated in solid portions of the tumor tissue to papillary projections extending into the clefts and glandlike spaces. The *third architectural design* that is noted in the more highly characteristic tumor is the reproduction of epitheliallike cells upon a supporting stroma of compact tissue, formed of elongated cells with small dark nuclei.

Treatment. (1) Accessible tumors, usually encapsulated, should be treated by *Widespread local excision.* Pathological examination will permit gradation of the tumor and allow a short period of observation. *Amputation* may be deferred to the time of the first recurrence but never beyond this.

(2) Inaccessible or unresectable tumors, such as those of intraarticular localization, should be treated by *immediate primary amputation.*

(3) *X-ray therapy* may retard the growth of some tumors and can be employed after local excisions.

I. MISCELLANEOUS

1. Paget's Disease. *Etiology.* The *etiology* of Paget's disease is *entirely obscure* and the fact that the lesions are not generalized but spotty in distribution is strong evidence against the disturbance being on an endocrinological or metabolic basis.

Incidence. Past 40 or 50. Most frequent between 60 and 70. On rare occasions the lesion may manifest itself before the age of 40.

Schmorl noted that the disease is not infrequently present in limited form and may even be subclinical. *It may be limited to one or two vertebrae or to part of the sacrum and show no clinical changes. He found that about 3 percent of the subjects past 40 showed some evidence of Paget's disease.*

X-Ray Picture. In the roentgenogram the *affected bone is enlarged,* the *cortex is thickened,* and the *trabeculae stand out prominently.* There are often areas of lessened density interspersed in the dense cortical bone or in the medullary cavity. These may resemble cysts.

In the *skull* there is *marked thickening,* usually at *first* of the *outer table,* with later involvement of the inner. The diploe are involved with the outer table. *A coarsely mottled appearance is produced by dense rounded, knoblike areas interspersed with areas of lessened density.*

Osteoporosis Circumscripta: The lesion is characterized by *large circumscribed areas sharply demarcated in the skull.* The lesions may be single of variable extent, or multiple. There may be a few dense areas in the osteoporotic portion.

Pathology—Gross. The *initial lesion* in Paget's disease is *bone destruction,* the *cause* of this being *entirely obscure.* The resultant weakness of the involved bones renders them less resistant to stresses and strains, and this leads to a *stimulation of the osteoblasts and an overproduction of bone. In*

The repair of bone by the osteoblasts is never completed, since the localized initial disorder causing bone destruction apparently persists. There results alternating destruction and repair of bone, which eventually leads to the *pathognomonic pathological finding*, the so-called *"mosaic structure." This mosaic appearance is due to the highly irreglar cement lines, each one of which demarcates a place where bone destruction temporarily ceased and bone repair began.*

The increased bone destruction and bone repair seen in the lesions of Paget's disease are closely similar to those seen throughout the skeleton in the osteitis fibrosa generalisata of hyperparathyroidism. There is one important difference, however; in osteitis fibrosa generalisata, that bone is destroyed that can best be spared; in Paget's disease, bone is destroyed without regard to structure. This accounts for the complete lack of arrangement in the cement lines and for the *fact that the bones in Paget's disease are extremely pliable in spite of marked overgrowth of bone.*

Tubular bones are thickened, softened, and bent, resulting in saber tibia, bowing legs, coxa vara, deformities of the spine and pelvis, and thickening of the skull.

Microscopically there is first a replacement of the original bone by *connective tissue,* and then a substitution of finely porous cancellous bone which gradually becomes harder. Absorption and apposition go on together, but the latter outstrips the former so that the bone becomes thick though still finely porous. One of the most characteristic features of the microscopic picture is the *great number and irregular arrangement of the lamellar systems,* which is seen in no other disease of bone. This gives what is known as a mosaic structure, due to variously shaped areas of new and old bone fitted together like pieces in a jigsaw puzzle. These pieces are not arranged around vascular canals to form Haversian systems. The cement lines are wide, prominent and irregularly scalloped. Occasional giant cells may be seen.

If a bone containing Paget's disease is immobilized as after a fracture, the following events occur: A *lack of stress and strain,* in all probability abetted by the *alarm reaction of Selye,* curbs the overactivity of the osteoblasts, and the *serum phosphatase level,* an index of bone formation, *falls.* The initial disturbance causing bone destruction persists. There results a *marked imbalance between bone destruction and bone formation.* The *increased calcium and phosphorus* coming from the bone leads by *hypercalciuria and hyperphosphaturia.* The capacity of the *kidney* to excrete calcium may be *overtaxed,* with a resulting *hypercalcemia; if fluids are not forced, if the diet is not kept low in calcium, and if immobilization is not kept at a minimum, a so-called chemical death from hypercalcemia may supervene.*

[illegible] In the advanced polyostotic [illegible] *[illegible]matous degeneration may be* [illegible] [illegible] Paget's disease in its various forms, including all cases, the incidence is *considerably less than 10 percent.* The conversion of Paget's disease into sarcoma does not necessarily imply that the tumor is an osteogenic sarcoma, as can be seen in those specimens which are malignant and which show only proliferating spindle cells without any tendency to new bone formation.

Diagnosis. The diagnostic aids consist of X-ray examination and the determination of the serum alkaline phosphatase, which is usually increased—often markedly so. The monostotic form may have a normal alkaline phosphatase.

2. Eosinophilic Granuloma. *Eosinophilic granuloma of bone, Letterer-Siwe disease, and Schüller-Christian disease constitute different clinical expressions of the same basic disorder, which seems to have a predilection for the hemopoietic system.* Its lesions apparently represent a peculiar inflammatory reaction to some as yet *unknown infectious agent* and are characterized cytologically at their start by the presence of *large numbers of histiocytes.*

Histologically, the lesion is characterized by *sheetlike collections of histiocytes, interspersed among which there are more or less prominent accumulations or eosinophilic cells.* There may also be occasional fields of hemorrhage and necrosis, and, in relation to these fields, larger or smaller numbers of multinuclear giant cells may be present.

Mallory classifies these diseases as follows:

a. The disorder may manifest itself in infancy or very early childhood in an often rapidly fatal form in which the histiocytic lesions are widely distributed both through the soft tissues and the skeleton (*Letterer-Siwe disease*).

b. The disorder may appear in children or adults in a chronic form in which the histiocytic lesions, again usually not limited to the skeleton, tend to undergo collagenization and lipidization, and in which the prognosis is often still grave because of the likelihood of damage to the lungs and heart and to the brain and pituitary gland (*Schüller-Christian disease, or lipogranulomatosis*).

c. The disorder may appear in children or young adults in a comparatively *benign* and much *more localized form* in which the *lesions* seem to *occur only in the skeleton* (and often only in a single bone), heal readily after simple curettage, and may indeed heal by resolution even without any therapeutic intervention (*eosinophilic granuloma of bone*).

Clinical and X-Ray Features of Eosinophilic Granuloma of Bone. Any bone may be involved; the humerus and femur are common sites. When multiple bones are involved, the cranial vault, some of the ribs, and one or more of the vertebrae may be sites of the disease. *In the laboratory, a leukocytosis of a moderate degree may be present,* and, in *occasional cases, the differential count may show a slight increase of the eosinophilic leukocytes. Roentgenographically,* the individual lesion of bone presents itself as a *small or a large radiolucent zone. In the long bones, the lesion begins to evolve in the interior of the bone,* and, as it enlarges to implicate the neighboring *cortex,* the latter becomes *eroded from the inside. The cortex may become expanded and even perforated,* and, where perforation has taken place, *deposition of periosteal new bone may be noted.* There is nothing distinctive about the X-ray appearance of the individual lesion, and *such conditions as a primary tumor, Brodie's abscess, and—where many bones are involved—metastatic growth, multiple myeloma, and Ewing's tumor should be ruled out.* In the presence of lesions in the skull, Schüller-Christian disease should be considered.

Treatment.

(1) The *lesion may undergo spontaneous resolution.*

(2) *Curettage.*

(3) *X-ray therapy.* After diagnosis has been ascertained, X-ray, therapy can be used to resolve this lesion.

3. Bone Cyst.

Etiology. The lesion has its basis in a *local disorder of development and bone growth.*

Solitary Cyst in Long Tubular Bones—Clinical Aspects—Age. It is the *period between early childhood and adolescence that the majority of patients come under observation,* although the condition may make itself manifest in adults.

Sex. Males are more commonly involved than females.

The cyst is usually quite advanced in its evolution before its presence is discovered. Pain following pathological fracture usually brings the condition to light after medical aid has been sought. *The most strongly favored bone site is the proximal portion of the humeral shaft, followed in order by the proximal portion of the femoral shaft. These two sites account for about two-thirds of the localizations of the lesion.*

X-Ray Picture. The cyst involves the upper metaphysis of the long bone (humerus or femur).

The *cyst* in a young subject *rarely, if ever, transgresses* the *epiphyseal cartilage plate.* A cyst developing in a long bone after fusion of the epiphysis with the shaft may present evidence of involvement of the shaft and the adjacent epiphyseal end of the bone. The *diameter* of the *shaft* in the affected region may be found *slightly expanded. The regional cortex appears somewhat thinned, the thinning taking place from the medullary surface.* The *affected area* of the shaft appears *somewhat rarefied* because of the disappearance of markings of the spongiosa. On occasion, the rarefied area may appear irregularly trabeculated. The trabeculae reflect the presence of ridges on the medullary surface of the cortex rather than walls traversing and dividing the cyst.

A cyst which extends to the immediate vicinity of, or abuts against, an epiphyseal cartilage plate should be regarded as an active one still possessing potentialities for growth. *A cyst which has definitely moved away from the plate,* so that a reconstructed area of shaft between it and the plate exists, has entered into the *latent stage,* for its *growth activity has ceased.* It is this *latent and static stage* of the cyst that *responds most promptly to curettage and packing with bone chips.*

Pathology—Gross. The *cortical wall* of the cyst is *thin* and quite translucent. A *clear fluid may be found within the cyst* if there has not been a fracture. The *cavity of the cyst is not divided* into compartments. The *inner surface* of the cortex is lined by a thin, smooth, gray-white *connective tissue membrane.*

Microscopic. Microscopic examination reveals that the *material curetted from the cyst consists mainly of fibrin clots,* often containing some red blood cells and undergoing organization. The *membrane* is *thin* in most places and *consists of connective tissue cells;* in other areas, the *membrane may be slightly thicker* and may consist of rather vascular connective tissue.

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active hyperemia which is manifested in osteoporosis of the living bone. This osteoporosis can occur only in the presence of a free blood supply, for the calcium is carried away by the blood stream. *Avascular bone cannot be decalcified; it retains its original calcium content.* It is for this reason that a seq [illegible]
and, [illegible]
differ [illegible]
necrotic area preserves its original density and it may even appear by contrast to be increased in density.

Stage of Regeneration. Active hyperemia of the neighboring bone initiates a growth of granulation tissue. Capillary loops and a fibrous stroma invade the necrotic area. Phagocytes, both multinuclear and mononuclear, resorb the dead marrow and grow along the Haversian canals, which become enlarged to several times their original size. They are followed by bone-forming cells, *and bone resorption and bone formation go on almost simultaneously. The Haversian canals are rebuilt,* layer upon layer, and they gradually resume their normal proportions. By this *"creeping substitution," both form and architecture are preserved.* The process is identical with that by which a bone graft, cut off from its circulation, is invaded and replaced by living bone. *The replacement may be traced radiographically by the decalcification which accompanies revascularization.* In the earlier stages the appearances often suggest fragmentation of the dead bone, because tonguelike inroads of vascular decalcified granulation tissue surround the islets of avascular dead bone. Similarly, localized areas of decalcification give an appearance of cyst formation.

Stages of Healing. Regeneration may occupy many months or even years. The newly formed bone is soft and easily distorted, but ultimately it regains the full strength of original bone. *Articular cartilage, on the other hand, suffers more permanent damage. It is largely replaced by fibrous tissue and fibrocartilage.* Early weight bearing encourages collapse of the subchondral bone, and it may be responsible for irregularity of the joint contours. Even if there is freedom from weight bearing, the new fibrocartilage is so imperfect that degenerative arthritis often develops.

6. Myositis Ossificans and Traumatic Subperiosteal Ossification. *Types.* (1) *Myositis ossificans progressiva.* This disorder is of *congenital origin,* and there is a constant association with *congenital shortening of the great toe.* There are recurrent inflammatory attacks in fibrous tissue planes leading to ossification in tendons and in the fibrous intersections of muscles. All the skeletal muscles are ultimately involved; the spine becomes rigid, and every affected joint is ankylosed. The disease progresses steadily and it is not amenable to any known treatment.

(2) *Heterotopic ossification.* It has been reported in semilunar cartilages, in abdominal scars and in the tendo achillis.

(3) *"Myositis ossificans traumatica"* (traumatic subperiosteal ossification).

Etiology. Trauma.

Pathogenesis and Pathology:

(1) Severe deep muscle contusion.
(2) hemorrhage with accompanying inflammatory reaction.

Treatment. Curettage of the cyst and the *insertion of autogenous bone chips* is the *treatment of choice.* Occasionally in cysts still abutting against the cartilage plate, large cystic areas may reappear after curettage.

4. Osteoid Osteoma. Osteoid osteoma is a *distinctive benign tumor* appearing in bones. It is always a small lesion affecting a single bone.

Etiology. Unknown. Has a predilection for adolescents and young adults, although it may affect any age group.

Clinical Features. The presenting symptom is *localized pain,* usually of at least several months' duration, which may be persistent and severe enough to wake the patient at night.

Location. It may develop in the *spongiosa* or in the *cortex* of the affected bone, and it stands out from the surrounding osseous tissue as a *sharply delimited ridus.* The *latter is usually composed of osteoid and more or less calcified atypical new bone,* which can be seen to have developed out of a rather vascular osteogenic connective tissue.

Pathology. An osteoid osteoma seems to run the following histogenetic course: It appears to pass from (a) *an initial stage,* in which actively proliferating and compacted osteoblasts may be prominent, through (b) *an intermediate phase,* in which osteoid in various stages of calcification is conspicuous, to (c) *the mature stage, in which the prominent feature of the lesion is the presence of densified trabeculae of highly calcified atypical bone.* When an osteoid osteoma develops in spongiosa, a narrow or even fairly wide zone of the surrounding spongy osseous tissue usually becomes densified and sclerotic; if an osteoid osteoma develops in cortex, the latter, too, tends to become thickened, mainly through periosteal new bone deposition.

X-Ray. The X-ray picture has two aspects: The manifestation of the osteoid osteoma proper and that of the reaction which it has incited in the surrounding tissue. The *osteoid osteoma proper* is usually indicated roentgenographically by a *relatively radiolucent or rarefied area;* although, if it has become substantially ossified, it may appear as a relatively radiopaque nidus. In the *cortex* of a long bone, one may have difficulty in distinguishing the osteoid osteoma shadow if the reactive cortical thickening is considerable or if the lesion has become ossified, since its shadow may be dominated by that of the thickened cortex.

Treatment. Surgical excision of the osteoid osteoma proper with some of the surrounding bone is the procedure of choice.

5. Avascular Necrosis. Avascular necrosis occurs in many areas of the skeletal system and a detailed discussion of the various examples of avascular necrosis may be found in the bibliography. The following represents in brief essay form the general picture of aseptic necrosis.

Onset of Necrosis. There is *immediate cellular death* of the avascular tissues. The *marrow elements change* to a *formless debris, bone cells disintegrate,* and *lacunae* become *empty.* When a joint surface is involved, patches of necrosis appear, separated by areas where articular cartilage has survived by direct nutrition from the synovial fluid. The general architecture of the bone remains undisturbed so that the radiographic appearances are unchanged. Shortly, however, *a neighboring bone reacts with an*

In tuberculosis of the spine, the *infection is usually confined to the vertebral bodies,* although occasionally the transverse processes or posterior arches may be primarily or secondarily involved. The tuberculous process within the vertebral bodies results in the breaking down of one to several adjacent vertebrae with relatively *little or no new bone formation. Wedge-shaped collapse follows. Destruction of the bony cortex adjacent to the intervertebral disk produces secondary changes in the fibrocartilaginous disk which leads to a narrowing of the intervertebral space. Roentgenologically, loss of the shadow of bony articular cortex, narrowing of the intervertebral space, and collapse of the vertebral bodies are seen.* Collapse of the vertebral bodies with preservation of intervertebral space and the shadow of articular cortex is indicative of malignancy rather than tuberculosis, as are also areas of involvement at several different levels of the spine. In active tuberculous destruction of the spine, *caseous material may accumulate beneath the paravertebral ligaments producing, when partially calcified, a fusiform paravertebral shadow in the roentgenogram.* In the lumbar region, partially calcified cold abscesses, which have migrated downward in the psoas fascia, are sometimes seen. Involvement of adjacent vertebrae by the tuberculous infection usually takes place by the direct extension of tuberculous material which infects adjacent vertebrae and, if the infection is severe may result in wedge-shaped areas of necrosis in the vertebral bodies. Involvement of a large number of vertebrae by direct extension is common in the dorsal spine, where dense ligaments prevent escape of the cold abscess.

8. Pyogenic Osteomyelitis. *Pathologic Changes. An understanding of the pathology is essential for the correct roentgenologic interpretation of the changes in osteomyelitis.* The *infection* most frequently *begins* in the metaphysis. It *occasionally arises* somewhere along the *course of periosteal* or *endosteal surface* of the shaft and, *very rarely,* in the *epiphysis.* The *changes* consist in *vascular congestion, edema, necrosis, leukocytic infiltration,* and *pus formation.* In some cases, the disease remains *localized,* but usually the involvement is *diffuse.* The *exudate* spreads along the *medullary canal* for varying distances and *usually penetrates the cortex, accumulating beneath the periosteum and separating it from the bone to an extremely variable extent.* The *necrosis* involves *cancellous bone* and a *variable amount of cortex.* It may be limited to one end or it may extend the entire length of the diaphysis in a part or all of its circumference. The disease may become *localized in 10 days to 2 weeks,* but in *severe cases it may spread for a much longer time.*

The *reparative changes* become very active on the subsidence of the acute infection and are *accomplished by the activity of osteoblasts, osteoclasts,* and *pyogenic granulation tissue. They may be considered under three heads:* (1) *Changes in necrotic bone,* (2) *formation of new bone,* and (3) *changes in the old living bone.*

(*1*) *In Necrotic Bone.* The *dead bone* is *absorbed* by the action of *granulation tissue* which develops about its surface. *Absorption takes place earliest and most rapidly at the junction of dead and living bone.* If the *dead bone is small in amount, it is entirely destroyed by granulation tissue, leaving behind a cavity. Necrotic cancellous bone* in localized osteomyelitis

(3) hematoma absorption, in which stage *ossification* takes place. The latter occurs during the healing stage and not during the acute hemorrhagic and inflammatory stage.

7. Tuberculosis of Bones. Tuberculosis of bones may be either *primary* or *secondary,* by direct extension from a primary tuberculous arthritis. *Primary osseous tuberculosis is relatively more frequent during childhood than in adult life. In the long bones of children* it begins most frequently in the metaphysis. *In late childhood and adolescence it may be primary in the epiphysis, but primary tuberculous epiphysitis is rare in young children. The epiphyseal lesions always give rise to arthritis, and the metaphyseal lesions usually do so.*

In infants and young children, there may be *diffuse involvement* of the *diaphysis* of the bone. *This lesion usually begins in a metaphysis* and *spreads to the rest of the diaphysis,* but in some instances the primary lesion may be located anywhere along the course of the shaft.

The metacarpals, metatarsals, and phalanges are most frequently affected, but the large bones of the extremities are occasionally the seat of involvement. *Primary infection of the body of the vertebra* is a *common lesion during childhood.* There may be a direct spread of the infection to adjacent vertebrae. Other bones of the trunk and the skull bones are occasionally involved. The *tarsal bones,* particularly the *os calcis,* may be the seat of primary osseous tuberculosis, but the carpal bones are rarely involved primarily.

In adults, the most frequent seat of tuberculosis of bones is the epiphysis of long bones; this affection gives rise to tuberculous arthritis. Adults affected with tuberculosis elsewhere, as of the lungs, not infrequently develop tuberculous osteitis. *The spine, ribs, skull, and, occasionally, the metaphyses of the long bones may become involved. Diffuse tuberculous osteomyelitis involving the shaft of a large bone is rare.* Less than 50 cases were reported prior to 1946. Occasionally it is seen in a metacarpal or phalanx, producing *spina ventosa. Secondary tuberculosis of the end of the bone,* resulting from primary tuberculous arthritis, is also not uncommon in adults. As the joint structure is broken down, the disease may invade the bone on one or both sides of the joint, producing large areas of necrosis which may even extend into the metaphysis. Tuberculous arthritis may extend to the periosteum, producing more or less new bone along the surface of the end of the shaft and the side of the epiphysis. *Tuberculous tenosynovitis in the hand may extend to the carpals, metacarpals, or phalanges, as was observed in two cases in this clinic.*

Massive necrosis in osseous tuberculosis is not uncommon in the end of the bone and may be followed by the formation of sequestra which border on the joint. It is rare in the course of the shaft of long bones. Caries sicca is an unusual form of tuberculosis, in which bone is killed and absorbed by tuberculous granulation tissue without caseation and liquefaction. Cold abscess formation may occur in connection with primary tuberculosis of any location, but it is usually more frequent and more extensive when there is associated joint involvement.

In tuberculosis of the spine, the *infection is usually confined to the vertebral bodies,* although occasionally the transverse processes or posterior arches may be primarily or secondarily involved. The tuberculous process within the vertebral bodies results in the breaking down of one to several adjacent vertebrae with relatively *little or no new bone formation. Wedge-shaped collapse follows. Destruction of the bony cortex adjacent to the intervertebral disk produces secondary changes in the fibrocartilaginous disk which leads to a narrowing of the intervertebral space. Roentgenologically, loss of the shadow of bony articular cortex, narrowing of the intervertebral space, and collapse of the vertebral bodies are seen.* Collapse of the vertebral bodies with preservation of intervertebral space and the shadow of articular cortex is indicative of malignancy rather than tuberculosis, as are also areas of involvement at several different levels of the spine. In active tuberculous destruction of the spine, *caseous material may accumulate beneath the paravertebral ligaments producing, when partially calcified, a fusiform paravertebral shadow in the roentgenogram.* In the lumbar region, partially calcified cold abscesses, which have migrated downward in the psoas fascia, are sometimes seen. Involvement of adjacent vertebrae by the tuberculous infection usually takes place by the direct extension of tuberculous material which infects adjacent vertebrae and, if the infection is severe may result in wedge-shaped areas of necrosis in the vertebral bodies. Involvement of a large number of vertebrae by direct extension is common in the dorsal spine, where dense ligaments prevent escape of the cold abscess.

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The *reparative changes* become very active on the subsidence of the acute infection and are *accomplished by the activity of osteoblasts, osteoclasts,* and *pyogenic granulation tissue. They may be considered under three heads:* (1) *Changes in necrotic bone,* (2) *formation of new bone,* and (3) *changes in the old living bone.*

(1) *In Necrotic Bone.* The *dead bone* is *absorbed* by the action of *granulation tissue* which develops about its surface. *Absorption takes place earliest and most rapidly at the junction of dead and living bone.* If the *dead bone is small in amount, it is entirely destroyed by granulation tissue, leaving behind* [illegible] *cavity. Necrotic cancellous bone* in localized osteomyelitis

is *usually all absorbed,* even though extensive in amount. *Dead cortex* in *appreciable amount* is gradually detached from living bone to form a *sequestrum. Lines of a sequestrum are usually jagged and irregular.* The organic elements present throughout dead bone are largely broken down by the action of the proteolytic ferments of the exudate. Because of loss of blood supply, the dead bone is whiter than living bone. *The time required for separation is variable according to the density and thickness of the involved bone.*

Spongy bone is *absorbed rapidly* and may be completely sequestrated or destroyed in from *2 to3 weeks,* but *necrotic cortex* may require from *2 weeks to 6 months for separation, depending on its size and thickness and on the general condition of the patient.* After complete sequestration, the dead bone is less readily attacked by granulation tissue and more slowly absorbed. The *rate of absorption is greater when the dead bone is surrounded by an involucrum.* When free in a pocket or located along a discharging sinus, there is practically no absorption, since healthy granulations do not come in contact with it. The fracture surfaces of dead fragment ends in compound fractures usually show no sign of erosion. When periosteum is extensively killed and no involucrum forms over the dead bone, its surface may remain uneroded for long periods. The same may be true of the endosteal surface when the shaft is destroyed in the greater part or all of the circumference. Healthy granulations cannot come in contact with it, and even the cancellous bone may be found intact years after the occurrence of necrosis.

(2) *New Bone Formation. New bone forms from the surviving portions of periosteum, endosteum,* and *cortex in the region of the infection.* It may be laid down along both periosteal and endosteal surfaces. *The surviving periosteum about the dead bone forms an involucrum which gradually increases in density and thickness to form part or all of the new shaft.* This is continuous with new bone formed on the end of the cortex which is not killed by the infection. Recurrence of infection may result in the formation of superimposed layers of involucrum, and *cloacae* are *present at the points where periosteum has been killed.* The new bone increases in amount and density for weeks or months, according to the size of the bone and extent and duration of the infection. The endosteal new bone may obstruct the medullary canal at the limits of the infection. *After the discharge or removal of sequestra, the remaining cavity may be filled out with new bone. This is especially apt to be the case in children. However, in adults, particularly when the walls are dense, the cavities are likely to persist.* In some instances, the space may become filled with fibrous tissue or it may be lined with fibrous tissue and communicate with the outside by means of a discharging sinus. Large *cavities of long standing may become lined with* [illegible]

[illegible]

of inflammatory reaction which permeates it. After subsidence of the infection and resumption of function of the part, its density increases again and

it may undergo extensive transformation to meet the new lines of stress and strain resulting from loss of substance of the shaft. Eventually it may be difficult to distinguish between the old living bone and the newly formed bone. *Areas of chronic infection frequently persist in the old living bone and are responsible for recurrences months or years after healing has taken place.* In other cases, especially in children, the infection is completely overcome, and the bone becomes so transformed that years afterwards all traces of the disease have disappeared.

Localized Osteomyelitis. In localized osteomyelitis involving either cancellous bone or cortex, the dead bone is usually all absorbed within a few weeks, leaving a cavity filled with granulation tissue and pus. There is a variable amount of new bone laid down about it. When the cavity is located in the metaphysis the surrounding new bone is usually either small or medium in amount, but, when located along the thicker portions of shaft, it is nearly always relatively extensive. *When destruction is limited and new bone formation abundant,* the condition is often designated as *sclerosing osteomyelitis.*

Epiphysitis. Primary hematogenous pyogenic infection of the growing epiphysis is an *extremely rare condition.* Secondary involvement of the epiphysis may occur as a result of primary metaphysitis by direct extension through the cartilaginous disk. It may result in cavity formation, or in some locations, as in the head of the femur, the entire epiphysis may become necrotic.

Joint Involvement. Acute pyogenic arthritis is the most common complication of osteomyelitis. It usually results from direct extension of the infection of the synovia of the joint. The infection varies from serous to purulent, and, when severe, it has a tendency to break down the articular cartilage and cortex at the point of greatest contact and pressure. This may result in fibrous or bony ankylosis, depending on the degree of surface destruction. *When the disease spreads to the joint by way of the epiphysis, a joint sequestrum* may be formed which has *greater density than the surrounding living bone, and its articular cortex is intact, but with cartilage destroyed.*

Appendix A

OUTLINE OF COURSE OF STUDY

Recently, the American Board of Orthopaedic Surgery, Inc., ruled that a 6-month period of study of the basic sciences would be required in the training of applicants for certification by the Board. The major portion of this time should be devoted to anatomy and pathology, with biochemistry, bacteriology, and physiology receiving attention for shorter periods.

The accompanying outline has been prepared as a guide in the administration of a course of study in the basic sciences designed to satisfy these requirements.

It is recommended that during the first 13 weeks of training each basic science fellow or resident prepare a paper concerning a subject studied during that period. The paper should include a comprehensive review of the literature and should concern itself mainly with a discussion of material related to orthopedics.

It is further recommended that during the second half of the 6-month period a paper on pathology be written which should include the history, physical findings, X-ray reports, and gross and microscopic findings of several orthopedic cases.

FIRST WEEK

	A.M.		P.M.	
Monday	8-12	Anatomy. inguinal region, gluteal region, upper thigh.	1-2:30	Orthopedic X-ray conference.
Tuesday	8-12	Anatomy same.	1-2.30	Clinical orthopedic conference.
Wednesday	8-12	Anatomy same.	1-2	Orthopedic significance of part studied.
Thursday	8-12	Anatomy: same.	3-4.30	Physiology: physiology of articular structures.
Friday	8-12	Anatomy. same.	3-5	Surgical approaches of part studied, by orthopedic surgeons.

SECOND WEEK

Monday	8-12	Anatomy: hip joint.	1-2.30	Orthopedic X-ray conference.
Tuesday	8-12	Anatomy· same.	1-2.30	Clinical orthopedic conference.
Wednesday	8-12	Anatomy: same.	1-2	Orthopedic significance of part studied.
Thursday	8-12	Anatomy: same.	3-4:30	Physiology: shock and burns.
Friday	8-12	Anatomy: same.	3-5	Surgical approaches of part studied, by orthopedic surgeons.

THIRD WEEK

Monday	8-12	Anatomy· thigh and knee.	1-2.30	Orthopedic X-ray conference.
Tuesday	8-12	Anatomy: same.	1-2 30	Clinical orthopedic conference.
Wednesday	8-12	Anatomy: same.	1-2	Orthopedic significance of part studied.
Thursday	8-12	Anatomy. same.	3-4:30	Physiology: blood substitutes.
Friday	8-12	Anatomy: same.	3-5	Surgical approaches of part studied, by orthopedic surgeons.

FOURTH WEEK

Monday	8-12	Anatomy: leg and ankle	1-2:30	Orthopedic X-ray conference.
Tuesday	8-12	Anatomy: same	1-2.30	Clinical orthopedic conference.
Wednesday	8-12	Anatomy: same	1-2	Orthopedic significance of part studied.
Thursday	8-12	Anatomy: same	3-4:30	Physiology: wound healing.
Friday	8-12	Anatomy: same	3-5	Surgical approaches of part studied, by orthopedic surgeons.

FIFTH WEEK

Monday	8-12	Anatomy: foot	1-2:30	Orthopedic X-ray conference.
Tuesday	8-12	Anatomy, same	1-2.30	Clinical orthopedic conference.
Wednesday	8-12	Anatomy: same	1-2	Orthopedic significance of part studied.
Thursday	8-12	Anatomy: same	3-4:30	Physiology: protein in surgical patients
Friday	8-12	Anatomy: same	3-5	Surgical approaches of part studied, by orthopedic surgeons.

SIXTH WEEK

Monday	8-12	Anatomy: neck and brachial plexus.	1-2.30	Orthopedic X-ray conference.
Tuesday	8-12	Anatomy: same	1-2:30	Clinical orthopedic conference.
Wednesday	8-12	Anatomy: same	1-2	Orthopedic significance of part studied.
Thursday	8-12	Anatomy: same	3-4:30	Physiology: water balance.
Friday	8-12	Anatomy: same	3-5	Surgical approaches of part studied, by orthopedic surgeons.

SEVENTH WEEK

Monday	8-12	Anatomy: shoulder	1-2.30	Orthopedic X-ray conference.
Tuesday	8-12	Anatomy. same	1-2.30	Clinical orthopedic conference.
Wednesday	8-12	Anatomy: same	1-2	Orthopedic significance of part studied
Thursday	8-12	Anatomy: same	3-4:30	Physiology: respiration
Friday	8-12	Anatomy. same	3-5	Surgical approaches of part studied, by orthopedic surgeons

EIGHTH WEEK

Monday	8-12	Anatomy arm and elbow	1-2.30	Orthopedic X-ray conference
Tuesday	8-12	Anatomy same	1-2.30	Clinical orthopedic conference
Wednesday	8-12	Anatomy: same	1-2	Orthopedic significance of part studied
Thursday	8-12	Anatomy: same	3-4:30	Physiology: blood studies
Friday	8-12	Anatomy: same	3-5	Surgical approaches of part studied, by orthopedic surgeons

NINTH WEEK

Monday	8-12	Anatomy: forearm and wrist.	1-2.30	Orthopedic X-ray conference
Tuesday	8-12	Anatomy. same	1-2.30	Clinical orthopedic conference
Wednesday	8-12	Anatomy same	1-2	Orthopedic significance of part studied
Thursday	8-12	Anatomy: same	3-4.30	Physiology: muscle metabolism
Friday	8-12	Anatomy. same	3-5	Surgical approaches of part studied, by orthopedic surgeons

TENTH WEEK

Monday	8-12	Anatomy: hand	1-2 30	Orthopedic X-ray conference
Tuesday	8-12	Anatomy. same	1-2.30	Clinical orthopedic conference
Wednesday	8-12	Anatomy: same	1-2	Orthopedic significance of part studied
Thursday	8-12	Anatomy: same	3-4.30	Physiology: autonomic nervous system
Friday	8-12	Anatomy: same	3-5	Surgical approaches of part studied, by orthopedic surgeons

ELEVENTH WEEK

Monday	8-12	Anatomy back	1-2:30	Orthopedic X-ray conference.
Tuesday	8-12	Anatomy same	1-2.30	Clinical orthopedic conference.
Wednesday	8-12	Anatomy: same	1-2	Orthopedic significance of part studied.
Thursday	8-12	Anatomy: same	3-4.30	Physiology: kidney function.
Friday	8-12	Anatomy same	3-5	Surgical approaches of part studied, by orthopedic surgeons.

TWELFTH WEEK

Day	Time	Subject	Time	Subject
Monday	8-12	Anatomy: review	1-2:30	Orthopedic X-ray conference.
Tuesday	8-12	Anatomy: review	1-2.30	Clinical orthopedic conference.
Wednesday	8-12	Anatomy: review	1-2	Review of orthopedic significance of parts studied.
Thursday	8-12	Anatomy: review	3-4:30	Physiology: acid-base balance.
Friday	8-12	Anatomy: review	3-5	Review of surgical approaches.

THIRTEENTH WEEK

Day	Time	Subject	Time	Subject
Monday	8-12	Anatomy: review	1-2:30	Orthopedic X-ray conference.
Tuesday	8-12	Anatomy: review	1-2:30	Clinical orthopedic conference.
Wednesday	8-12	Anatomy: review	1-2	Review of orthopedic significance.
Thursday	8-12	Anatomy: review	3-4.30	Physiology: vitamins in surgery.
Friday	8-12	Anatomy: review	3-5	Review of surgical approaches.

FOURTEENTH WEEK

(In the study and discussion of bone tumors, the classification recommended by the Tumor Registry of the American College of Surgeons will be followed.)

Day	Time	Subject	Time	Subject
Monday	9-12	Pathology: preparation of sections and specimens.	1-2:30	Pathology lecture on subject studied in laboratory.
Tuesday	*9-12*	*Pathology: same*	*1-2:30*	*Clinical orthopedic conference.*
Wednesday	9-12	Pathology: same	4-5	Bacteriology: introduction.
Thursday	9-12	Pathology: same	1-2:30	Orthopedic X-ray conference.
Friday	9-12	Pathology: same	4-5	Biochemistry and pharmacology: chemistry of protein, carbohydrate, and fat.

FIFTEENTH WEEK

Day	Time	Subject	Time	Subject
Monday	9-12	Pathology: normal bone growth and repair.	1-2:30	Pathology lecture on subject studied in laboratory.
Tuesday	9-12	Pathology: same	1-2:30	Clinical orthopedic conference.
Wednesday	9-12	Pathology: same	4-5	Bacteriology: environmental influences on bacteria.
Thursday	9-12	Pathology: same	1-2.30	Orthopedic X-ray conference.
Friday	9-12	Pathology: same	4-5	Biochemistry and pharmacology: calcium, phosphorus and phosphatase metabolism.

SIXTEENTH WEEK

Day	Time	Subject	Time	Subject
Monday	9-12	Pathology: bone tumors	1-2:30	Pathology lecture on subject studied in laboratory.
Tuesday	9-12	Pathology: same	1-2:30	Clinical orthopedic conference
Wednesday	9-12	Pathology: same	4-5	Bacteriology. transmission of bacteria.
Thursday	9-12	Pathology: same	1-2:30	Orthopedic X-ray conference.
Friday	9-12	Pathology	4-5	Biochemistry and pharmacology: calcium, phosphorus and phosphatase metabolism.

SEVENTEENTH WEEK

Day	Time	Subject	Time	Subject
Monday	9-12	Pathology: bone tumors.	1-2.30	Pathology lecture on subject studied in laboratory.
Tuesday	9-12	Pathology: same	1-2:30	Clinical orthopedic conference.
Wednesday	9-12	Pathology: same	4-5	Bacteriology. bacteriology of skin and respiratory tract.
Thursday	9-12	Pathology: same	1-2:30	Orthopedic X-ray conference
Friday	9-12	Pathology: same	4-5	Biochemistry and pharmacology: calcium, phosphorus and phosphatase metabolism

EIGHTEENTH WEEK

Day	Time	Subject	Time	Subject
Monday	9-12	Pathology: bone tumors	1-2.30	Pathology lecture on subject studied in laboratory.
Tuesday	9-12	Pathology: same	1-2.30	Clinical orthopedic conference.
Wednesday	9-12	Pathology: same	4-5	Bacteriology: bacteriology of mouth and gastrointestinal tract.
Thursday	9-12	Pathology: same	1-2:30	Orthopedic X-ray conference.
Friday	9-12	Pathology: same	4-5	Biochemistry and pharmacology: isotopes.

FOURTH WEEK

Monday	8-12	Anatomy: leg and ankle	1-2:30	Orthopedic X-ray conference.
Tuesday	8-12	Anatomy: same	1-2:30	Clinical orthopedic conference.
Wednesday	8-12	Anatomy: same	1-2	Orthopedic significance of part studied.
Thursday	8-12	Anatomy: same	3-4:30	Physiology: wound healing.
Friday	8-12	Anatomy: same	3-5	Surgical approaches of part studied, by orthopedic surgeons.

FIFTH WEEK

Monday	8-12	Anatomy: foot	1-2:30	Orthopedic X-ray conference.
Tuesday	8-12	Anatomy: same	1-2:30	Clinical orthopedic conference.
Wednesday	8-12	Anatomy: same	1-2	Orthopedic significance of part studied.
Thursday	8-12	Anatomy: same	3-4:30	Physiology: protein in surgical patients.
Friday	8-12	Anatomy: same	3-5	Surgical approaches of part studied, by orthopedic surgeons.

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Monday	8-12	Anatomy: neck and brachial plexus.	1-2:30	Orthopedic X-ray conference.
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Wednesday	8-12	Anatomy: same	1-2	Orthopedic significance of part studied.
Thursday	8-12	Anatomy: same	3-4:30	Physiology: water balance.
Friday	8-12	Anatomy: same	3-5	Surgical approaches of part studied, by orthopedic surgeons.

SEVENTH WEEK

Monday	8-12	Anatomy: shoulder	1-2:30	Orthopedic X-ray conference.
Tuesday	8-12	Anatomy: same	1-2:30	Clinical orthopedic conference.
Wednesday	8-12	Anatomy: same	1-2	Orthopedic significance of part studied
Thursday	8-12	Anatomy: same	3-4:30	Physiology: respiration
Friday	8-12	Anatomy: same	3-5	Surgical approaches of part studied, by orthopedic surgeons

EIGHTH WEEK

Monday	8-12	Anatomy: arm and elbow	1-2:30	Orthopedic X-ray conference
Tuesday	8-12	Anatomy: same	1-2:30	Clinical orthopedic conference
Wednesday	8-12	Anatomy: same	1-2	Orthopedic significance of part studied
Thursday	8-12	Anatomy: same	3-4:30	Physiology: blood studies
Friday	8-12	Anatomy: same	3-5	Surgical approaches of part studied, by orthopedic surgeons

NINTH WEEK

Monday	8-12	Anatomy: forearm and wrist.	1-2:30	Orthopedic X-ray conference
Tuesday	8-12	Anatomy: same	1-2:30	Clinical orthopedic conference
Wednesday	8-12	Anatomy: same	1-2	Orthopedic significance of part studied
Thursday	8-12	Anatomy: same	3-4:30	Physiology: muscle metabolism
Friday	8-12	Anatomy: same	3-5	Surgical approaches of part studied, by orthopedic surgeons

TENTH WEEK

Monday	8-12	Anatomy: hand	1-2:30	Orthopedic X-ray conference
Tuesday	8-12	Anatomy: same	1-2:30	Clinical orthopedic conference
Wednesday	8-12	Anatomy: same	1-2	Orthopedic significance of part studied
Thursday	8-12	Anatomy: same	3-4:30	Physiology: autonomic nervous system
Friday	8-12	Anatomy: same	3-5	Surgical approaches of part studied, by orthopedic surgeons

ELEVENTH WEEK

Monday	8-12	Anatomy: back	1-2:30	Orthopedic X-ray conference.
Tuesday	8-12	Anatomy: same	1-2:30	Clinical orthopedic conference.
Wednesday	8-12	Anatomy: same	1-2	Orthopedic significance of part studied.
Thursday	8-12	Anatomy: same	3-4:30	Physiology: kidney function.
Friday	8-12	Anatomy: same	3-5	Surgical approaches of part studied, by orthopedic surgeons.

TWELFTH WEEK

Day	Morning	Afternoon
Monday	8-12 Anatomy: review	1-2:30 Orthopedic X-ray conference.
Tuesday	8-12 Anatomy: review	1-2.30 Clinical orthopedic conference.
Wednesday	8-12 Anatomy: review	1-2 Review of orthopedic significance of parts studied.
Thursday	8-12 Anatomy: review	3-4:30 Physiology: acid base balance.
Friday	8-12 Anatomy: review	3-5 Review of surgical approaches.

THIRTEENTH WEEK

Day	Morning	Afternoon
Monday	8-12 Anatomy: review	1-2:30 Orthopedic X-ray conference.
Tuesday	8-12 Anatomy: review	1-2:30 Clinical orthopedic conference.
Wednesday	8-12 Anatomy: review	1-2 Review of orthopedic significance.
Thursday	8-12 Anatomy: review	3-4.30 Physiology: vitamins in surgery.
Friday	8-12 Anatomy: review	3-5 Review of surgical approaches.

FOURTEENTH WEEK

(In the study and discussion of bone tumors, the classification recommended by the Tumor Registry of the American College of Surgeons will be followed.)

Day	Morning	Afternoon
Monday	9-12 Pathology: preparation of sections and specimens.	1-2:30 Pathology lecture on subject studied in laboratory.
Tuesday	9-12 Pathology: same	1-2:30 Clinical orthopedic conference.
Wednesday	9-12 Pathology: same	4-5 Bacteriology: introduction.
Thursday	9-12 Pathology: same	1-2:30 Orthopedic X-ray conference.
Friday	9-12 Pathology: same	4-5 Biochemistry and pharmacology: chemistry of protein, carbohydrate, and fat.

FIFTEENTH WEEK

Day	Morning	Afternoon
Monday	9-12 Pathology: normal bone growth and repair.	1-2:30 Pathology lecture on subject studied in laboratory.
Tuesday	9-12 Pathology: same	1-2:30 Clinical orthopedic conference.
Wednesday	9-12 Pathology: same	4-5 Bacteriology: environmental influences on bacteria.
Thursday	9-12 Pathology: same	1-2.30 Orthopedic X-ray conference.
Friday	9-12 Pathology: same	4-5 Biochemistry and pharmacology: calcium, phosphorus and phosphatase metabolism.

SIXTEENTH WEEK

Day	Morning	Afternoon
Monday	9-12 Pathology: bone tumors	1-2:30 Pathology lecture on subject studied in laboratory.
Tuesday	9-12 Pathology: same	1-2:30 Clinical orthopedic conference.
Wednesday	9-12 Pathology: same	4-5 Bacteriology: transmission of bacteria.
Thursday	9-12 Pathology: same	1-2:30 Orthopedic X-ray conference.
Friday	9-12 Pathology	4-5 Biochemistry and pharmacology: calcium, phosphorus and phosphatase metabolism.

SEVENTEENTH WEEK

Day	Morning	Afternoon
Monday	9-12 Pathology: bone tumors.	1-2:30 Pathology lecture on subject studied in laboratory.
Tuesday	9-12 Pathology. same	1-2:30 Clinical orthopedic conference.
Wednesday	9-12 Pathology: same	4-5 Bacteriology: bacteriology of skin and respiratory tract.
Thursday	9-12 Pathology: same	1-2:30 Orthopedic X-ray conference.
Friday	9-12 Pathology: same	4-5 Biochemistry and pharmacology: calcium, phosphorus and phosphatase metabolism

EIGHTEENTH WEEK

Day	Morning	Afternoon
Monday	9-12 Pathology bone tumors	1-2:30 Pathology lecture on subject studied in laboratory.
Tuesday	9-12 Pathology. same	1-2:30 Clinical orthopedic conference.
Wednesday	9-12 Pathology. same	4-5 Bacteriology: bacteriology of mouth and gastrointestinal tract.
Thursday	9-12 Pathology: same	1-2:30 Orthopedic X-ray conference.
Friday	9-12 Pathology: same	4-5 Biochemistry and pharmacology: isotopes.

NINETEENTH WEEK

Monday	9-12	Pathology: bone tumors	1-2:30	Pathology lecture on subject studied in laboratory.
Tuesday	9-12	Pathology: same	1-2:30	Clinical orthopedic conference.
Wednesday	9-12	Pathology: same	4-5	Bacteriology: bacteriology of genitourinary tract.
Thursday	9-12	Pathology: same	1-2:30	Orthopedic X-ray conference.
Friday	9-12	Pathology: same	4-5	Biochemistry and pharmacology: enzyme systems.

TWENTIETH WEEK

Monday	9-12	Pathology: bone tumors	1-2:30	Pathology lecture on subject studied in laboratory.
Tuesday	9-12	Pathology: same	1-2:30	Clinical orthopedic conference.
Wednesday	9-12	Pathology: same	4-5	Bacteriology: immunity.
Thursday	9-12	Pathology: same	1-2:30	Orthopedic X-ray conference.
Friday	9-12	Pathology: same	4-5	Biochemistry and pharmacology: vitamins and their chemical effects in tissues.

TWENTY-FIRST WEEK

Monday	9-12	Pathology: systematized anomalies of skeletal development.	1-2:30	Pathology lecture on subject studied in laboratory.
Tuesday	9-12	Pathology: same	1-2:30	Clinical orthopedic conference.
Wednesday	9-12	Pathology: same	4-5	Bacteriology: antitoxins.
Thursday	9-12	Pathology: same	1-2:30	Orthopedic X-ray conference.
Friday	9-12	Pathology: same	4-5	Biochemistry and pharmacology: antibiotics and chemotherapy.

TWENTY-SECOND WEEK

Monday	9-12	Pathology: skeletal changes produced by vitamin deficiency, by endocrine disorders; arthritides.	1-2:30	Pathology lecture on subject studied in laboratory.
Tuesday	9-12	Pathology: same	1-2:30	Clinical orthopedic conference.
Wednesday	9-12	Pathology: same	4-5	Bacteriology: agglutinins, opsonins, and active immunization.
Thursday	9-12	Pathology: same	1-2:30	Orthopedic X-ray conference.
Friday	9-12	Pathology: same	4-5	Biochemistry and pharmacology: antibiotics and chemotherapy.

TWENTY-THIRD WEEK

Monday	9-12	Pathology: diseases of lipoid metabolism, purine metabolism; diseases of synovia, tendon sheaths and bursae.	1-2:30	Pathology lecture on subject studied in laboratory.
Tuesday	9-12	Pathology: same	1-2:30	Clinical orthopedic conference.
Wednesday	9-12	Pathology: same	4-5	Bacteriology: allergy.
Thursday	9-12	Pathology: same	1-2:30	Orthopedic X-ray conference.
Friday	9-12	Pathology: same	4-5	Biochemistry and pharmacology: antibiotics and chemotherapy.

TWENTY-FOURTH WEEK

Monday	9-12	Pathology: Paget's disease, eosinophilic granuloma of bone, Schüller - Christian disease, Letterer-Siwe disease.	1-2:30	Pathology lecture on subject studied in laboratory.
Tuesday	9-12	Pathology: same	1-2:30	Clinical orthopedic conference.
Wednesday	9-12	Pathology: same		
Thursday	9-12	Pathology: same	1-2:30	Orthopedic X-ray conference.
Friday	9-12	Pathology: same	4-5	Biochemistry and pharmacology: antibiotics and chemotherapy.

TWENTY-FIFTH WEEK

Monday	9-12	Pathology: bone cyst, osteoid osteoma, avascular necrosis, myositis ossificans.	1-2:30	Pathology lecture on subject studied in laboratory.
Tuesday	9-12	Pathology: same	1-2:30	Clinical orthopedic conference.
Wednesday	9-12	Pathology: same		
Thursday	9-12	Pathology: same	1-2:30	Orthopedic X-ray conference.
Friday	9-12	Pathology: same	4-5	Biochemistry and pharmacology: pharmacology of anesthetic agents.

TWENTY-SIXTH WEEK

Monday	9-12	Pathology: tuberculosis of long bones, osteomyelitis, osteomalacia and osteoporosis, syphilitic bone changes.	1-2:30	Pathology lecture on subject studied in laboratory.
Tuesday	9-12	Pathology: same	1-2:30	Clinical orthopedic conference.
Wednesday	9-12	Pathology: same		
Thursday	9-12	Pathology: same	1-2:30	Orthopedic X-ray conference.
Friday	9-12	Pathology	4-5	Biochemistry and pharmacology: pharmacology of anesthetic agents.

Appendix B

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